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CLINICAL USE OF A NEW ANTIHISTAMINIC COMPOUND (PYRIBENZAMINE) IN CERTAIN CUTANEOUS DISORDERS

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IN 1927 Lewis [1] postulated that allergic reactions depend on or are produced by the liberation of a histamine-like substance (H substance) at the site of the reaction. Most investigators are of the opinion that histamine and the H substance are identical or nearly so. Many investigators have sought ways and means of neutralizing this H substance and thus preventing the sequence of events that occurs in allergic reactions. In 1932 Hill and Martin [2] reviewed the literature on antihistaminic substances and methods of preventing anaphylactic shock that had been described up to that time. None of these methods were effective. Since then, however, rapid progress has been made along this line.

Fourneau and Bovet, in 1933,[3] pointed out that the drug thymoxyethyldiethylamine (929 F) had the ability to counteract the effects of histamine both in vitro and in vivo. Subsequently, this phenolic ether and others were studied for their antihistaminic effects by Bovet and Staub and their co-workers.[4] This chemical and one other were found

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The pyribenzamine used in this study was furnished through the courtesy of Ciba Pharmaceutical Products, Inc., of Summit, N. J.

1. Lewis, T.: The Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, Ltd., 1927.

2. Hill, J. H., and Martin, L.: Review of Experimental Studies of Non-Specific Inhibition of Anaphylactic Shock, Medicine **11**:141-223 (May) 1932.

3. Fourneau, E., and Bovet, D.: Recherches sur l'action sympathicolytique d'un nouveau dérivé du dioxane, Arch. internat. de pharmacodyn. et de thérap. **46**:178-191 (Oct. 15) 1933; abstracted, Compt. rend. Soc. de biol. **113**:388-390, 1933.

4. Bovet, D., and Staub, A. M.: Action protectrice des ethers phénoliques au cours de l'intoxication histaminique, Compt. rend. Soc. de biol. **124**:547-549, 1937. Staub, A. M., and Bovet, D.: Action de la thymoxyethyldiethylamine (929 F) et des éthers phénoliques sur le choc anaphylactique du cobaye, ibid. **125**:818-821, 1937. Ungar, G.; Parrot, J. L., and Bovet, D.: Inhibition des

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to be the most effective of the group in the prevention of histaminic and anaphylactoid reactions in guinea pigs. The first of these, thymoxyethyldiethylamine (929 F), was identical with that of Fourneau and Bovet. The second, N,-phenyl-N-ethyl-N′-diethylethylenediamine, was called 1571 F and was found by Staub to be more effective than 929 F. These drugs, known as the Fourneau antihistaminic preparations, have been studied by a number of American authors, particularly Loew and his co-workers.[5] Wilcox and Seegal,[6] Rosenthal and Brown,[7] Rosenthal and Lambert[8] and others[9] have confirmed the findings of Staub and her co-workers. The Fourneau antihistaminic drugs, although effective in preventing the sequence of events which histamine produces in tissue, were too toxic for human use. They led, however, to the development by Halpern,[10] in 1942, of a drug called "antergan," which chemically is dimethylaminoethylbenzylaniline (2339 RP). This drug has been used clinically in European countries and has been reported on by Parrot,[11] DeCourt,[12] Célice and Durel,[13] Schnitzer,[14]

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effets de l'histamine sur l'intestin isolé du cobaye par quelques substances sympathicomimetiques et sympathicolytiques, ibid. **124**:445-446, 1937. Staub, A. M.: Recherches sur quelques bases synthétiques antagonistes de l'histamine, Ann. Inst. Pasteur **63**:400-436 (Oct.) 1939.

5. Loew, E. R.; Kaiser, M. E., and Moore, V.: Synthetic Benzhydryl Alkamine Ethers Effective in Preventing Fatal Experimental Asthma in Guinea Pigs Exposed to Atomized Histamine, J. Pharmacol. & Exper. Therap. **83**:120-129 (Feb.) 1945.

6. Wilcox, H. B., and Seegal, B. C.: Influence of an Ethylendiamine Derivative on Histamine Intoxication and Anaphylactic Shock in the Intact Guinea Pig and the Isolated Guinea Pig Heart, J. Immunol. **44**:219-229 (July) 1942.

7. Rosenthal, S. R., and Brown, M. L.: Thymoxyethyldiethylamine as an Antagonist of Histamine and of Anaphylactic Reactions, J. Immunol. **38**:259-266 (April) 1940.

8. Lambert, E. H., and Rosenthal, S. R.: Liberation of a Histamine-like Substance on Stimulation of Sympathetic Nerves, Proc. Soc. Exper. Biol. & Med. **44**:235-237 (May) 1940.

9. Climenko, D. R.; Homburger, E., and Messer, F. H.: Pharmacology of Thymoxyethyldiethylamine, J. Lab. & Clin. Med. **27**:289-297 (Dec.) 1941.

10. Halpern, B. N., cited by Mayer, R. L.: Substances with Anti-Histamine Activity, to be published.

11. Parrot, J. L.: Syndromes histaminiques et antagonistes de l'histamine, Presse méd. **50**:771-772 (Dec. 19) 1942.

12. DeCourt, P.: Traitement de l'asthme par des bases antagonistes de l'histamine, Presse méd. **50**:773-774 (Dec. 19) 1942.

12. DeCourt, P.: Traitement de l'asthme par des bases antagonistes de l'histamine, Presse méd. **50**:773-774 (Dec. 19) 1942.

13. Célice, J., and Durel, P.: Eruptions sériques et antihistaminiques de synthèse, Ann. de dermat. et syph. (Bull. Soc. franç de dermat. et syph.) **2**:370 (July-Aug.) 1942.

14. Schnitzer, A.: Clinical and Experimental Experiences with Antergan, an Antihistamine Preparation, Dermatologica **91**:92-101, 1945.

Gordonoff [15] and others. The drug was effective in urticaria, some types of asthma, serum sickness and other clinical manifestations of allergy. Certain side effects were noted such as restlessness, excitement, sleeplessness, accelerated heart beat, drug fever, apprehension, exanthemas and oliguria.

More recently Loew and his co-workers [16] in this country have studied a group of synthetic benzhydryl alkamine ethers. Two of these benzhydryl alkamine ethers were found to be far superior to the Fourneau antihistaminic compounds. They were nontoxic to guinea pigs and were capable of preventing the majority of animals from dying after exposure to atomized histamine. Oral administration was found to be effective. One of these drugs, beta-dimethylaminoethyl benzhydryl ether hydrochloride, was prepared for clinical use in human beings and has been marketed under the name benadryl. Among the American authors reporting clinical investigations on this drug are O'Leary and Farber,[17] Shaffer and co-workers,[18] Curtis and Owens,[19] Logan [20] and McElin and Horton.[21] O'Leary and Farber reported that 9 out of 15 patients with acute urticaria received almost complete relief and 5 others improved. There was one failure. In chronic urticaria, 25 out of 35 patients received almost complete relief, while 7 were improved and 3 were not benefited. Shaffer and associates reported that 7 out of 8 patients with urticaria were benefited. Curtis and Owens stated that 11 out of 18 patients with acute urticaria secured decided relief, 3 patients with chronic urticaria were improved and 4 received little or no benefit. Shaffer and colleagues stated that 1 patient with atopic dermatitis was relieved but that the drug had no effect on neurodermatitis or dyshidrotic eczema. Logan employed benadryl in treating allergic

15. Gordonoff, T.: The Anti-Allergic Action of Antergan, Schweiz. med. Wchnschr. **74**:639-696 (June) 1944.

16. (*a*) Loew, E. R.; Kaiser, M. E., and Moore, V.: Effects of Various Drugs on Experimental Asthma Produced in Guinea Pigs by Exposure to Atomized Histamine, J. Pharmacol. & Exper. Therap. **86**:1-6 (Jan.) 1946. (*b*) Loew, E. R.; MacMillan, R., and Kaiser, M. E.: The Antihistaminic Properties of Benadryl (B-Di Methyl Amino Ethyl) Benhydryl Ether Hydrochloride, ibid. **86**:229-238 (March) 1946. (*c*) Loew, Kaiser and Moore.[5]

17. O'Leary, P. A., and Farber, E. M.: Benadryl in Treatment of Urticaria, Proc. Staff Meet., Mayo Clin. **20**:429-432 (Nov. 14) 1945.

18. Shaffer, L. W.; Carrick, L., and Zackheim, H. S.: Use of Benadryl for Urticaria and Related Dermatoses: Preliminary Report, Arch. Dermat. & Syph. **52**:243-245 (Oct.) 1945.

19. Curtis, A. C., and Owens, B. B.: Beta Di Methylaminoethyl Benzhydryl Ether Hydrochloride (Benadryl) in Treatment of Urticaria, Arch. Dermat. & Syph. **52**:239-242 (Oct.) 1945.

20. Logan, G. B.: The Use of Benadryl in Treating Some of the Allergic Diseases of Childhood, Proc. Staff Meet., Mayo Clin. **20**:436-438 (Nov. 14) 1945.

21. McElin, T. W., and Horton, B. T.: Clinical Observations on the Use of Benadryl: A New Antihistamine Substance, Proc. Staff Meet., Mayo Clin. **20**: 417-429 (Nov. 14) 1945.

diseases of childhood and reported that 9 out of 12 patients with seasonal hay fever had excellent or good results, while there was a questionable result in 1 and no effect in another. In his series, bronchial asthma was not affected, and in urticaria and vasomotor rhinitis the drug had a palliative effect. All these authors reported rather frequent mild to serious side effects from the administration of benadryl. O'Leary and Farber had 18 patients out of 50 in which symptoms from the drug developed, whereas McElin and Horton noted that in 54 patients out of a total of 74 who received benadryl orally, there developed side effects, and in one third of their patients receiving benadryl intravenously there developed symptoms from the drug. The commonest symptoms were sleeplessness, dizziness, dry mouth, nervousness, urinary frequency, epigastric distress, vomiting, weakness, vertigo, drowsiness and muscular pains. None of the authors reported any serious reactions to the drug.

A new group of compounds has recently been prepared by Mayer, Huttrer and Scholz.[22] These are known chemically as pyridylethylenediamines. One of these (N′ pyridil-N′ benzyl-N-dimethylethylenediamine) was called pyribenzamine. These authors found that this drug neutralized the effects of histamine on an isolated strip of guinea pig intestine. It was found effective against histamine-induced asthma in guinea pigs and against anaphylactic shock produced by the injection of horse serum in guinea pigs. The antianaphylactic and antihistaminic activity and toxicity of this drug were studied by Rennick, Chess, Hays, Mathieson, Mayer and Yonkman.[23] The drug was found effective against intratracheal injections of histamine in guinea pigs. Wheals produced by the intracutaneous injection of histamine in rabbits could be prevented by the intravenous administration of the drug or by gastric instillation. The drug was relatively nontoxic for white mice, white rats and rabbits, and human beings tolerated the drug well. Hays and

22. Mayer, R. L.; Huttrer, C. P., and Scholz, C. R.: Antihistaminic and Antianaphylactic Activity of Some A-Pyridino-Ethylenediamines, Science **102**: 93-94 (July 27) 1945; Federation Proc. **4**:129 (March) 1945.

23. Rennick, B.; Chess, D.; Hays, H. W.; Mathieson, D.; Mayer, R. H., and Yonkman, F. F.: The Antianaphylactic and Antihistaminic Activity and Toxicity of N′-Pyridyl-N′-Benzyl-N-Diethyl-Ethylenediamine HCL, Federation Proc. **4**:133-134 (March) 1945. Yonkman, F. F.; Chess, D.; Mathieson, D., and Hansen, N.: The Antihistaminic Action of N′-Pyridyl-N′-Benzyl-N-Dimethyl-Ethylenediamine HCL. (63c) in Relation to Salivation, Retraction of the Nictitating Membrane, Mydriasis, Lachrymation and Blood Pressure in Cats, ibid. **4**:143 (March) 1945. Yonkman, F. F.; Hays, H. W., and Rennick, B.: The Protective Action of N′-Pyridyl-N′-Benzyl-N-Dimethyl-Ethylenediamine HCL (63C) Against Horse Serum Anaphylaxis in Dogs, ibid. **4**:144 (March) 1945. Mathieson, D.; Hays, H. W.; Chess, D.; Cameron, A., and Yonkman, F. F.: Acute and Chronic Toxicity Studies of Pyribenzamine HCL (N-Pyridyl-N′-Benzyl-N-Dimethyl-Ethylenediamine HCL), ibid., to be published.

Rennick found that the drug protected against horse serum anaphylaxis in dogs in 50 per cent of cases. The drug administered to white rats for a period of five months showed no deleterious effects on the erythrocytes, white cells, hematocrit values, body weight, appetite, reproductive capacities, gastrointestinal functions or general appearance.

Mayer [24] has reviewed the literature on substances with specific antihistaminic activity, and he has compared the activity of these various related chemical compounds. Loew and his co-workers compared the action of benadryl with 1571 F. From an experimental laboratory standpoint, the action of pyribenzamine and benadryl has been compared with the action of 1571 F and 929 F by means of four principal laboratory experiments, as follows: (1) neutralization of the effect of histamine on guinea pig intestine, (2) neutralization of the effect of intravenously injected histamine, (3) prevention of anaphylactic shock and (4) determination of the effect on histamine-induced asthma. In regard to the first experiment, with guinea pig intestine, Loew [25] found that benadryl was fifteen to twenty times as effective as 1571 F. Mayer found that pyribenzamine was one to ten thousand times as effective as 929 F. Since it was well known that 1571 F was approximately 25 per cent more effective than 929 F, it is apparent from these analogous experiments that pyribenzamine is far more effective than benadryl. As regards the second experiment, with intravenously injected histamine, benadryl was found to be twice as effective as 1571 F, whereas pyribenzamine was twenty to twenty-five times as effective as 1571 F, and it might be added that antergan was found to be ten times as effective as 1571 F. Here again pyribenzamine demonstrated its superiority. Concerning the third experiment, on prevention of anaphylactic shock, it did not appear from the work of Loew and Kaiser [25a] that benadryl was much more effective than 1571 F, while Mayer demonstrated that pyribenzamine was two to three hundred times as effective as 1571 F. Finally, as regards the fourth experiment, on histamine-induced asthma, Loew and his co-workers [5] found benadryl twice as effective as 1571 F. Mayer demonstrated that pyribenzamine was several times more effective than 1571 F. In summary, according to comparative laboratory experiments which Mayer [24] and others have done with pyribenzamine and antergan and Loew and his co-workers with benadryl, pyribenzamine apparently stands superior, antergan second and benadryl third.

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24. Mayer, R. L.: Substances with Specific Antihistaminic Activity, J. Allergy, to be published.

25. (*a*) Loew, E. R., and Kaiser, M. E.: Alleviation of Anaphylactic Shock in Guinea Pigs wth Synthetic Benhydryl Alkamine Ethers, Proc. Soc. Exper. Biol. & Med. **58**:235-237 (March) 1945. (*b*) Loew, Kaiser and Moore.[16a]

Arbesman, Koepf and Miller [26] have reported recently that in studies on guinea pigs and human beings histamine wheals showed a definite decrease after the administration of 50 to 150 mg. of pyribenzamine orally in 14 out of 22 patients. Four out of 6 allergic patients showed a definite decrease in the size of histamine-induced wheals. Twenty-four patients were tested with a series of allergens and retested forty-five minutes after receiving 100 mg. of pyribenzamine orally. Fourteen of the 24 showed a definite decrease in the size of the wheals following the use of pyribenzamine. Reactions in passively sensitized areas of skin were also decreased by pyribenzamine. Koepf, Arbesman and Munafo,[27] in studies of toxicity in dogs, noticed no serious toxic effects. Arbesman, Koepf and Lenzner [28] have recently reported on a clinical study of 277 patients with various allergic disorders. The average adult dose varied from 100 to 400 mg. daily; the average dose for children was half that amount. As much as 1,200 mg. of pyribenzamine was given in twenty-four hours without any serious untoward effects. All medication was given orally. There was no effect on blood components, blood pressure or urine. Pyribenzamine prevented constitutional reactions from allergens to which the patients were sensitive, including urticarial reactions. Twenty-three of 24 patients with allergic rhinitis due to grass pollens were relieved of their symptoms, and 88 per cent of patients with ragweed hay fever were relieved. Seven of 16 patients with bronchial asthma associated with hay fever obtained relief from the asthma. Eighteen of 34 patients with perennial allergic rhinitis of extrinsic origin were relieved; 6 of 14 with perennial intrinsic rhinitis were relieved; 9 of 24 patients with extrinsic bronchial, seasonal asthma were relieved, and only 1 of 4 with intrinsic bronchial asthma was relieved. Fourteen out of 15 patients with acute urticaria were relieved, and 33 of 44 patients with chronic urticaria were benefited. They noted that several patients with atopic dermatitis obtained rather decided relief from pruritus when taking the drug. In 3 patients with urticaria due to hypersensitivity to cold, urticaria failed to develop on exposure to cold while they were taking the drug. In regard to drug reactions, in 66 per cent of their patients no symptoms developed; only 5.4 per cent discontinued the drug because of undesirable side effects. The commonest of these were sedation, drowsiness and fatigue. A few patients complained of dizziness, faintness and headache and, on rare occasions,

26. Arbesman, C. E.; Koepf, G. F., and Miller, G. E.: Some Antianaphylactic Properties of Pyribenzamine N′-Pyridyl-N′-Benzyl-Dimethyl-Ethylenediamine-Mono-Hydrochloride, J. Allergy, to be published.

27. Koepf, G. F.; Arbesman, C. E., and Munafo, C.: Chronic Toxicity of Pyribenzamine (N′-Pyridyl-N′-Benzyl-Dimethyl-Ethylenediamine-Mono-Hydrochloride), J. Allergy, to be published.

28. Arbesman, C. E.; Koepf, G. F., and Lenzner, A. R.: Clinical Studies with Pyribenzamine, J. Allergy, to be published.

nausea associated with emesis. A few complained of dryness of the mouth, and in 1 dermatitis medicamentosa developed.

CLINICAL STUDIES

In this paper, we wish to report the effects of pyribenzamine on patients presenting various cutaneous disorders and also the effect of the drug on wheals produced by the intradermal injection of allergens in patients with atopic dermatitis. A total of 122 patients was given the drug, and of these 89 were followed sufficiently long so that we could evaluate the effects of the drug.

Acute Urticaria.—There were 34 patients with acute urticaria. The follow-up was satisfactory in 24 of these. Pyribenzamine, in doses from 100 to 400 mg. per day, was prescribed, and the drug was taken from two to fourteen days. Twenty-three of the 24 patients obtained prompt and definite relief of symptoms. It should be noted at this point that approximately the same percentage of patients obtained relief from benadryl. Nineteen of the 24 patients were improved 50 per cent within twenty-four hours and free of urticaria in less than ten days. Four patients were at least 50 per cent improved in four days and free of eruption in fourteen days. In 3 of the latter 4, the urticaria returned twenty-four hours after the drug was stopped but the urticaria was controlled by readministration. One patient with acute urticaria believed to be due to codeine in a cough syrup experienced no relief from the drug. This was our only failure in acute urticaria.

Chronic Urticaria.—Twenty-three patients with chronic urticaria were given pyribenzamine. The dose varied from 200 to 300 mg. per day, and the period during which the drug was taken varied from six days to six months. Fifteen of these patients were followed adequately. Nine of the 15 were definitely benefited, whereas 6 patients reported no relief of symptoms. This result is essentially the same as that obtained with benadryl. In 6 of the 9 patients benefited by the drug, a recurrence of the urticaria developed within twenty-four hours after use of the drug was discontinued, but they again experienced relief when the drug was readministered. One patient had had urticaria for four months and took 200 mg. of pyribenzamine daily for fourteen days; the symptoms completely disappeared within forty-eight hours and have not recurred.

Atopic Dermatitis (Investigative Studies).—Sixteen patients with a chronic atopic dermatitis were studied in order to determine the effects of pyribenzamine on wheals resulting from the intradermal injection of a series of allergens. The allergens used were sheep wool, mixed feathers, milk, cat hair and three dilutions of egg white. The wheals resulting from these intradermal injections were observed and measured

at the end of fifteen minutes. Patients were then given 100 mg. of pyribenzamine and one hour later were retested with the same allergens as those which produced positive reactions in the original test. Of the 16 patients who received the intradermal injections, in 15 wheals developed to one or more of the allergens. In 7 of the 15, pyribenzamine produced no demonstrable diminution in the size of the wheal. Eight of the fifteen showed a decrease in the size of the wheal of 33.3 per cent or more. Two of the 8, following the ingestion of pyribenzamine, had no wheals on the second series of tests. On the basis of these experiments, we were unable to predict the outcome of the clinical use of pyribenzamine in these patients.

Chronic Atopic Dermatitis (Effect of Pyribenzamine on Symptoms).—Thirty-five patients with chronic atopic dermatitis were given pyribenzamine in doses of from 100 to 400 mg. daily for periods which varied from two weeks to four months. In the case of children, the dose varied in proportion to the body weight. Thirty of these patients were followed sufficiently long to determine the effects of pyribenzamine on the course of their disease. Nineteen of the 30 received definite relief of pruritus to the extent of at least 50 per cent. Three of the 19 experienced relief of pruritus within twenty-four hours. The remaining 16 patients were decidedly improved within a two week interval. In 16 of the 19 patients, itching recurred when the drug was stopped and was again relieved when the drug was readministered. In 3 of the 19 patients, the dermatitis disappeared within six weeks and has not recurred to date. It must be stated that all these patients received the usual routine treatment with topical applications and advice regarding the avoidance of common water-soluble protein allergens. Some patients deliberately stopped taking the drug or their supply ran out, and these patients felt that there was a prompt flare-up of the itching. Four of the 7 patients who showed no change in allergen-induced wheals after receiving 100 mg. of pyribenzamine were adequately followed. In 3 of these the pruritus was improved at least 50 per cent while taking the drug, and in 1 of these the eruption disappeared fifteen days after medication was started. There was, therefore, no correlation between the effects of pyribenzamine on allergen-induced wheals and clinical improvement. It was further noted that in the case of the 8 patients in whom pyribenzamine definitely diminished the size of allergen-induced wheals only 4 of these were benefited while taking the drug. This further demonstrated the lack of correlation between the effects of the drug on allergen-induced wheals and the results obtained clinically from the administration of the drug. It is our opinion that pyribenzamine is definitely palliative for approximately two thirds of the patients with chronic atopic dermatitis.

Dermatitis Venenata.—Fifteen patients with dermatitis venenata of long duration, most of whom were originally patients with industrial dermatitis, were given pyribenzamine in doses up to 400 mg. per day. In none of these did the drug appear to influence in any way the course of the eruption, nor did it produce any relief of symptoms.

Physical Allergy.—Two of our best results were in patients who presented examples of severe physical allergy of long duration. The first patient was a woman 50 years of age who had had severe sunlight urticaria for eighteen years. She had received medical attention from outstanding internists and had received every form of therapy known to us and to many other consulting dermatologists. Laboratory studies of every conceivable type had given uniformly normal results. On a trip to Florida the past winter, minimal exposure to bright sunlige produced the usual papular urticarial lesions. On each day thereafter, 100 mg. of pyribenzamine taken before and after exposing herself to sunlight for periods of from two to four hours completely prevented the development of urticarial lesions. Furthermore, the existing lesions, which usually healed in ten to fourteen days, disappeared within two to three days. Subsequent exposures to bright sunlight without pyribenzamine medication caused the usual urticarial lesions to appear. The second patient, a woman aged 53, had suffered from urticaria due to cold for thirty-three years. During this time, she had had countless episodes of giant urticaria involving all the exposed parts. Exposure to cold water, either in the tub or for purposes of swimming, had brought on collapse, with a loss of consciousness, on three occasions. Numerous allergy tests and attempts at desensitization had given unsuccessful results. She had been unable to eat ice cream for thirty-three years. She had had as many as twenty-two injections of epinephrine in a twenty-four hour period. Tests with small ice cubes produced erythema after fifteen seconds and severe urticaria after thirty seconds. Following the ingestion of 100 mg. of pyribenzamine, tests with small ice cubes showed extremely slight erythema at thirty seconds and only slight urticaria after sixty seconds. This patient has had complete relief by taking 50 to 100 mg. of pyribenzamine before exposing herself to cold in any form. For the first time in thirty-three years, she is able to eat a large dish of ice cream with impunity.

Dermatitis Herpetiformis.—Four patients with dermatitis herpetiformis disease have been followed sufficiently for us to draw conclusions regarding the effect of pyribenzamine on the course of their eruption. They received from 200 to 300 mg. of the drug daily. Three of the 4 patients had almost complete relief of pruritus and burning while taking the drug, and the eruption healed. After observation, however, we were not able to state that the relief was any greater than that

experienced following the ingestion of sulfapyridine although it was much more prompt.

Miscellaneous Conditions.—One patient with rather extensive insect bites secured prompt relief from itching following the administration of pyribenzamine.

REACTIONS TO PYRIBENZAMINE

In our experience reactions to pyribenzamine severe enough to be noted by the patient without suggestion were extremely rare. We purposely confined our questioning of the patients to one point, namely, whether they had noted unusual symptoms after the ingestion of the drug. Only 4 patients out of a total of 89 we were able to follow noted any disturbance. One patient complained of headache, another felt drowsy, 1 had nausea and the fourth had nausea and vomiting. The last patient was the only one that had to discontinue use of the drug, although he had taken it steadily for a period of four months. Our figures regarding reactions are certainly at variance with those of Koepf, Arbesman and associates. Part of this may be explained by the fact that we did not use, in general, as large doses as they employed. It is our opinion, from our own results and in comparison of reported reactions from benadryl in the literature, that reactions from the use of pyribenzamine are considerably less than those after use of benadryl when given in comparable dosage in the same type of case.

COMMENT

It is evident that the introduction of new antihistaminic compounds which can be administered by mouth has opened a totally new field in the palliative therapy of many allergic and allied diseases. We may expect further antihistaminic drugs to be introduced, perhaps far exceeding the value of our present preparations. So far, there are three antihistaminic compounds of outstanding merit, namely, antergan, benadryl and pyribenzamine. It is as yet too early to state which of these three drugs will eventually be shown to be superior from all standpoints. From an experimental laboratory standpoint and our own clinical experience, pyribenzamine appears to be the drug of choice.

CONCLUSION

1. Rapid progress has been made in the past thirteen years in the development of antihistaminic compounds. The three most effective compounds developed to date are antergan, benadryl and pyribenzamine.

2. Clinical studies on dermatologic conditions by various investigators indicate approximately the same degree of clinical benefit from each of the drugs. Almost all patients with acute urticaria are relieved, about two thirds of those with chronic urticaria are benefited and somewhat

more than one half of the patients with chronic atopic dermatitis are improved. Three out of 4 of our patients with dermatitis herpetiformis obtained relief.

3. In 2 cases of severe physical allergy pyribenzamine produced prompt and complete relief.

4. There did not seem to be any correlation between the effect of pyribenzamine on allergen-induced wheals and the clinical course of the patient after receiving pyribenzamine.

5. In our opinion, reactions to pyribenzamine are minimal and seldom necessitate stoppage of the drug.

ABSTRACT OF DISCUSSION

Dr. Hamilton Montgomery, Rochester, Minn.: The experience of my colleagues and me in the Department of Dermatology of the Mayo Clinic concurs and supports in the main what Dr. Osborne has said about pyribenzamine. Dr. O'Leary and Dr. Farber have recently reported their experience with patients with various types of cutaneous diseases treated with benadryl. Dr. Brunsting has reported on a series of 215 patients with various dermatoses treated with pyribenzamine. It is our impression that pyribenzamine is slightly superior to benadryl, because, although dose for dose they act about the same, the side reactions from benadryl are more frequent and severer than those from pyribenzamine. Dr. Brunsting's experience in cases of dermatitis venenata (contact dermatitis) differs from that of Dr. Osborne in that there were a good many cases in which there was some relief from the pruritus, but no significant influence was noted on the dermatitis per se. Five patients with dermatitis herpetiformis received no benefit from pyribenzamine. In patients in the early phases of acrosclerosis (scleroderma and Raynaud's disease), with either benadryl or pyribenzamine Dr. O'Leary obtained moderate temporary improvement in approximately 25 per cent of the cases, resulting in relaxation of the skin and restoration of some of the lost function of their fingers and hands. Both drugs are effective in relieving the symptoms of pruritus from urticaria in 85 to 90 per cent of the two series of cases. The response, however, is usually symptomatic and palliative and requires continued use of the drugs; however, an occasional patient is encountered who is apparently cured of chronic urticaria after using either drug for several weeks. The same effects are noted in angioneurotic edema. Pyribenzamine has a beneficial effect of producing slight drowsiness, which in itself is beneficial in obtaining relaxation in cases of urticaria. In the group with atopic eczema, a small percentage have derived relief from the severe paroxysms of pruritus. No doubt the soporific effect of the drugs also helps these patients through the recurring exacerbation.

Dr. Fred Wise, New York: When Dr. Osborne speaks of dermatitis venenata, does he refer to plant poisoning or contact dermatitis, or does he include both?

Dr. George C. Andrews, New York: In addition to the diseases that have been treated successfully by benadryl, I have been fortunate enough to have good results in the treatment of localized hyperhidrosis of the axilla and localized hyperhidrosis of the hands and also in erythema nodosum. In 2 cases the conditions cleared up in twenty-four hours, and as long as the patients took benadryl they were free from any symptoms or any nodules. I thought that it would be

interesting to add those two diseases to the list, particularly hyperhidrosis, which is such a difficult condition to cure.

One of the patients with hyperhidrosis was an x-ray technician and had had a great deal of roentgen ray therapy. She had been treated with diets and all kinds of remedies, including bromides and other sedatives. Nothing did her any good, but use of benadryl relieved her immediately.

DR. MARION B. SULZBERGER, New York: What I have to say is confirmation of what the presenters have said, with perhaps a few minor additions.

As Dr. Osborne said, this drug, pyribenzamine, was first introduced and studied by Dr. R. L. Mayer, a former assistant of Professor Jadassohn, who is a well trained dermatologist as well as an excellent chemist.

Because of my friendship with Mayer, he submitted this drug to me early; and both at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital and in the private practices of its staff members, pyribenzamine has now been given a trial on several hundred patients. There are just slight variations between our findings and those of Dr. Osborne and collaborators. In the few patients with dermatitis herpetiformis treated, we, like the physicians at the Mayo Clinic, were not particularly impressed with the benefits. It may be, however, that when a larger series has been treated these differences in results will be ironed out.

Again in adult atopic dermatitis we were not impressed, although an occasional patient did well. I had the impression that the earlier the case and the younger the disease, the better the results with pyribenzamine. But this drug is by no means the answer to the control of this disease or even the control of itching in this eruption. Only an exceptional patient with atopic dermatitis does really well; a few patients get moderate or questionable benefit, and many in our experience get no benefit whatsoever up to the limits of the tolerated doses.

I think that we are just at the beginning of a great development and will see significant advances in and wider application of drugs of this series. In my opinion, drugs of this type are going to be used in a large variety of chronic diseases; and in these diseases the patients will be taking these drugs more or less continuously, because these agents apparently allay the symptoms and reduce the manifestations without producing cures, as far as we can tell today. For this reason and because of the chemical and biologic attributes of these compounds, I think that it is necessary for patients taking these drugs to remain under constant and close medical control.

I think that if enough patients are treated with these drugs it is to be expected that in a few persons some more serious unoward effects (for example, of the type of blood dyscrasias) will be found sooner or later. It was the awareness of this possibility that limited the number of the patients included in our studies. We have not treated as many patients as we otherwise would, because we have made it a point to examine every patient once a week while taking the drug, including a complete blood cell count and differential count and examination of urine. I am convinced that, for the time being, all physicians should insist on this procedure. Otherwise, I am afraid that there may be unpleasant happenings for which we will be held responsible.

I should like to point out that there are many possible future uses of these drugs, as indicated by their trial in the sclerodermas and the acroscleroses, mentioned by Dr. Montgomery. In this connection, lupus erythematosus must be mentioned, and, in particular, the conditions which are definitely made worse by exposure to light. It is certainly conceivable that in such cases the use of this

drug might be indicated. I have just started treating 1 such patient and have as yet no results to report. There are many other cutaneous and internal diseases in which these agents might contribute a logical form of treatment. I shall mention only dermatomyositis (1 of our patients did well), many forms of drug reactions and periarteritis nodosa.

Another use of the drug is in cutaneous testing. It is known that when one is testing the skin for wheal reactions one sometimes cannot read the results of the test because of the dermographism. Each site tested produces a traumatic wheal. That traumatic wheal can be inhibited by adequate doses of pyribenzamine or benadryl, but the greater stimulus to whealing which is exercised by application of the allergen to which the patient is sensitive will usually break through the inhibitory action of those drugs. In this way, by a proper dose of one of these drugs, the false positive reactions due to traumatic whealing can be suppressed and the wheal reactions to the allergens will come through and can be recorded.

Dr. Richard S. Weiss, St. Louis: I should like to ask Dr. Osborne a question concerning the future supply of pyribenzamine. I tried to get a supply for experimental purposes but was informed that the company had only a limited amount for this purpose. I am glad to be informed that the drug is relatively nontoxic and hope that all of us will be able to use it shortly.

Dr. Earl D. Osborne, Buffalo: Time did not permit me to give some of the details, and I had to eliminate a great deal of the clinical work that has been done by Koepf and Arbesman. Dr. Sulzberger brought up the question of blood cell counts. Koepf and Arbesman have done all sorts of clinical and laboratory investigations in a large series of cases. Twelve hundred milligrams per day has been given without in any way affecting the laboratory tests. So far, at least, pyribenzamine has been shown to be of low toxicity to animals and human beings.

I think that it is important that we all read papers on this subject when they are published. Most of the work on this drug, by the way, is not yet published, except the work by Mayer and his associates. The other is in press now and will be out shortly.

One important thing about pyribenzamine and benadryl, too, is the way the drug is administered. Some men have the idea that all one has to do is to give 5 mg. every three or four hours. That may be all right in the chronic urticarias, but in treating atopic dermatitis we found it much better, since practically all the scratching and rubbing is at night, to give 100 mg. before retiring, and if the patient wakened during the night to give 100 mg. more and perhaps only 50 mg. two or three times during the day. Even that may not be necessary.

We were discouraged at first in atopic dermatitis. We felt that we were getting hardly any response, but after the passage of two or three weeks and the gradual reduction in the scratching index, as you might call it, those patients began to improve, and far more rapidly than would be naturally expected in the average case of atopic dermatitis. Our good results in atopic dermatitis vary from 50 per cent to 66.6 per cent.

Regarding the cases of dermatitis venenata, those were all cases of chronic industrial dermatitis.

In regard to hyperhidrosis, we had 1 patient who noticed prompt relief of hyperhidrosis, and Koepf and Arbesman have had a similar one.

DERMATOLOGIC PROBLEMS IN A STAGING AREA STATION HOSPITAL

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AND
LIEUTENANT COLONEL A. ALLEN GOLDBLOOM
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THE problems associated with the handling of diseases of the skin in a staging area station hospital are not of the type to which the average physician or dermatologist had previously become accustomed. To complicate further the care of the soldier in such a hospital, medical care and hospitalization had to be geared to the function of the camp. In this, the processing and subsequent departure of troops influenced treatment to a great degree. On arrival at the staging area from any part of the country, the soldier had just completed a train trip of perhaps one hundred and eight hours and was immediately processed preparatory to his departure. This frequently meant that any eruption not disabling or apparent was not treated by the soldier for almost a week. Then, when he was free from his numerous routine duties, the attention of the medical officer was called to a disease aggravated by neglect.

The dermatologic section at this station hospital was a part of the medical service and was under the supervision of a single medical officer, who was the chief of the section. The staff, although variable, was composed of two nurses, a trained civilian technician and at least two specially trained enlisted ward attendants.

Although the venereal section was a subdivision of the medical service, syphilitic patients were handled at this station hospital by the urologists, and therefore a report on them will not be included in this paper. In accordance with army procedure, all patients reported first on sick call each morning at their respective dispensaries, where the medical officer decided which ones were to be referred to the clinics and which admitted to the hospital. This weeded out many of those with minor dermatoses. The procedure has been that except in unquestionable cases no patient with a disease of the skin was admitted directly to the hospital without first being seen by the dermatologist. This eliminated many unnecessary hospitalizations.

From the Medical Service, Station Hospital, Camp Kilmer, N. J.

From its inception, in June 1942, until Sept. 1, 1945, this staging area station hospital admitted 52,788 patients, of whom 38,209 were admitted to the medical service. Of these, 2,968 had diseases of the skin. Thus 5.6 per cent of all the hospitalized patients and 7.7 per cent of all the patients hospitalized by the medical service were admitted to the dermatologic section. In addition to those of the inpatients service, 7,183 patients were seen during this period in the dermatologic outpatient clinic.

This series does not present a cross section of persons with dermatoses in the percentages usually expected in civilian practice. This is due partly to earlier elimination of persons with certain diseases of the skin by induction boards and in part to weeding-out of those with minor ailments by the dispensary surgeons—uncomplicated nondisabling diseases treated without a dermatologic consultation. The number of patients visiting the clinic was kept at a minimum by return visits being scheduled at intervals of at least seven to ten days unless the disease was of such a nature that a decided spread or exacerbation was to be anticipated. In this way, most of the patients seen were making their first visits. This enabled the dermatologist to devote more time to each patient, resulting in the eliciting of fuller histories and the making of thorough physical examinations.

In the staging area, as was mentioned earlier, problems were present, the chief of which was the early departure of the soldier for overseas duty. As in most army installations, the soldier either was or was not fit for duty. He was never placed "in quarters." The soldier seen for the first time after a week in camp presented a problem in therapy and judgment. The dermatologist knew that he would soon be asked whether this soldier could proceed with his unit, and time was of more than the usual importance. Because of this, every soldier was inspected by medical officers immediately on arrival and again forty-eight hours prior to departure. On this second inspection the officers frequently discovered dermatoses previously mild and recently aggravated and reported the patients for treatment just as the unit was preparing to depart. At this point it was the responsibility of the medical officer to the service to send all possible men with their units. It was also his duty to the man and his profession, however, not to send men who could not undertake the march with full equipment to the train, then to the ferry and from the ferry to the transport. In addition to the dermatologic problem present, the man's grade and importance to his unit had to be considered. It was many times more difficult to replace a trained technical sergeant than to replace a private. It was encouraging to see the morale of the units at the staging area station hospital just prior to departure to a combat area, when although the number

of men withdrawn was comparatively small most of them pleaded to be allowed to proceed with their units, despite severe diseases of the skin.

The dermatoses most commonly seen were chiefly of six types (table 1). The first six groups accounted for two thirds of all the patients hospitalized. Prior to Dec. 1, 1944, 723 patients with scabies were hospitalized, but since then there have been only 27 admitted to the hospital. The 1,200 patients with scabies seen in the clinic since then have been treated on an ambulatory status. This means that although the census since December 1944 may have been smaller it was made up of patients with severer dermatoses.

TABLE 1.—*Total Number of Hospitalized Patients with Commonest Dermatoses and Percentage of Total Number of Hospitalized Patients with Dermatoses*

Dermatoses	Patients	
	Total No. Hospitalized	Per-Cent of Total No. Hospitalized with Dermatoses
Scabies	750	25.3
Dermatophytoses, all types	488	16.4
Dermatitis venenata, all causes	338	11.0
Dermatitis, unclassified	188	6.3
Impetigo contagiosa	156	5.2
Dermatitis, eczematoid	133	4.4
Intertrigo, axilla or groin	79	2.6
Dermatitis, impetiginous	75	2.5
Urticaria, cause undetermined	65	2.2
Folliculitis, pustular	63	2.1
Dermatitis medicamentosa	51	1.7
Furunculosis	41	1.4
Dermatitis, allergic	39	1.3
Lichen simplex chronicus	32	1.0
Total	2498	83.4

In table 1 one notes that fourteen diagnoses made up 83.4 per cent of all dermatologic diseases of the patients admitted. The remaining 16.6 per cent comprised small numbers of the rarer diseases, such as the herpetiform and exfoliative dermatoses, ecthyma, epidermolysis bullosa, ichthyosis congenita, lupus erythematosus, molluscum contagiosum and keratosis punctata palmaris et plantaris, and also a few of the commoner diseases of patients who were admitted at night without the dermatologist's consultation, such as pityriasis rosea, psoriasis, herpes zoster and herpes simplex.

The admission of persons with certain types of dermatoses was almost routine. No one would hesitate to admit a person with severely infected dermatophytosis pedis or disseminated impetigo. On the other hand, the close living conditions and the inability of the men to carry out certain treatments in their barracks made admission obligatory for many men who in civilian life would ordinarily have been treated on an ambulatory status. For instance, a soldier had to be hospitalized

when he was unable to shave, when his face was covered with a white or black ointment or when a strong-smelling medicament, such as coal tar or sulfur, was used over a large area of his skin. Hospitalization was also necessary when wet dressings or frequent soaks were prescribed, since neither the time nor the facilities existed in the barracks for this type of treatment.

TABLE 2.—*Total Number of Patients with Commonest Dermatoses Discharged and Percentage of Total with that Disease and of Total Discharged*

Dermatoses	Total No.	% of Patients with Disease	% of Total Discharged
Lichen simplex chronicus	10	33.3	22.2
Dermatitis, unclassified	5	2.6	11.1
Dermatophytosis	5	1.0	11.1
Ichthyosis congenita	3	33.3	6.6
Dermatitis, seborrheic	3	37.5	6.6
Dermatitis, exfoliative	3	37.5	6.6
Dermatitis, allergic, due to wool	3	7.7	6.6
Urticaria, cause undetermined	2	3.1	4.4
Dermatitis, impetiginous	2	2.6	4.4
Dermatitis venenata, due to mercury	2	0.6	4.4
Other dermatoses, one each	7	...	16.0
Total	45	...	100.0

During the period from June 1942 to September 1945, 45 soldiers received medical discharges from the army because of a dermatologic ailment (table 2), and 116 failed to respond to therapy or presented such severe or widespread dermatoses that they could not be returned to duty in the sixty days allowed for treatment in a station hospital.

TABLE 3.—*Total Number of Patients with Commonest Dermatoses Transferred to Regional Hosiptals and Percentage of Total with Disease and of Total Transferred*

Dermatoses	Total No.	% of Patients with Disease	% of Total Transferred
Dermatitis, eczematoid	31	23.3	26.7
Dermatitis, unclassified	24	12.8	20.7
Dermatophytosis	24	4.9	20.7
Dermatitis, impetiginous	9	12.0	7.8
Acne vulgaris	4	44.4	3.4
Dermatitis, pustular	4	19.0	3.4
Folliculitis, pustular	3	4.8	2.6
Sycosis vulgaris	3	16.7	2.6
Toxic erythema	2	33.3	1.7
Dermatitis herpetiformis	2	13.3	1.7
Impetigo contagiosa	2	1.3	1.7
Other dermatoses, one each	8	...	7.0
Total	116	...	100.0

These were transferred to the designated regional hospitals for further observation and treatment (table 3). The chief disabling dermatologic diseases were dermatophytosis, eczematoid dermatitis and the unclassified dermatoses. These were found in 79 of the 116 transferred patients.

The 2 men who received medical discharges noted under dermatitis venenata were sensitive to mercury, present in the smoke resulting from the explosion of the percussion caps of cartridges and shells. The 3 men discharged with the diagnosis of allergic dermatitis were soldiers allergic to wool who could not be utilized in warmer climates where sun tan cotton uniforms were worn the year round.

The greatest therapeutic problem presented to the dermatologist in this staging area, as may be noted from table 1, was that of the dermatophytoses. There were 488 patients whose lower extremities chiefly were involved. This was 16.4 per cent of all patients hospitalized for dermatoses. Five patients with chronic and recurrent eruptions were given medical discharges while 24 were transferred to authorized regional hospitals. The results of treatment of persons previously hospitalized were discouraging. It was found that unless they were hospitalized early on the initial outbreak and given an adequate period of rest followed by a gradual return to full duty many had relapses almost immediately. To keep a soldier on duty with more than a mild dermatophytosis pedis was to invite a severe infection, possibly with a complicating dermatophytid of the hands and the development of a chronic eruption requiring many months to heal, if healing were to result at all. In general, the dermatologist has found that early hospitalization with rest in bed plus mild therapy was the treatment of choice and in the long run saved days of hospitalization in the management of this infection.

Another problem of general interest was that of the 133 soldiers with eczematoid dermatitis of the extremities. Among these cases, many eruptions of atopic origin were seen. Also, of this group, 10 men with complicating lichen simplex chronicus were discharged and 31 were transferred to regional hospitals. These, as may be noted from tables 1 and 2, head both lists. The neurogenic factors involved in this dermatitis have been recognized, and the army with its discipline and regimentation plus the idea of impending combat did much to aggravate the tendency toward this disease or the existing disease itself. It should be noted that of the 133 soldiers with eczematoid dermatitis 41 were not returned to duty within sixty days and ten of these were given medical discharges.

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KAPOSI'S VARICELLIFORM ERUPTION

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ST. PAUL
AND
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DES MOINES, IOWA

SINCE 1941 increased attention has been given to the cause of Kaposi's varicelliform eruption. Esser [1] and Seidenberg [2] in 1941 first contributed evidence that the virus of herpes simplex causes Kaposi's varicelliform eruption in at least some cases. Dermatologic attention has not previously been called to the publication by Esser, who described a small epidemic of this disease in an infants' ward, where 4 children became severely ill, 1 dying as a result of the infection. In 2 of Esser's cases the herpetic virus was recovered and identified by Seidenberg. Other investigators have since published reports of cases in which there has been suggestive or conclusive evidence incriminating the herpetic virus. Conditions of war kept the earlier reports from general attention of American dermatologists, but Barton and Brunsting [3] soon described the results of experimental studies in 2 cases of Kaposi's varicelliform eruption. At about the same time, Lynch observed the first of a series of cases in which clinical observation associated the herpetic virus with certain unusual eruptions. At a meeting in April 1944 he reported demonstration of the herpetic virus in a case in which the severity and extent of the eruption were not so great as is usual in Kaposi's disease.[4] Wenner, in April 1944, reported a case in a pediatric journal.[5] Lane and Herold subsequently observed a case of the disease in which Blattner,

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1. Esser, M.: Ueber eine kleine Epidemie von Pustulosis varioliformis acuta, Ann. pædiat. **157**:156, 1941.

2. Seidenberg, S.: Zur Aetiologie der Pustulosis vacciniformis acuta, Schweiz. Ztschr. f. Path. u. Bakt. **4**:398, 1941.

3. (*a*) Barton, R. L., and Brunsting, L. A.: Kaposi's Varicelliform Eruption: Report of Case, Proc. Staff Meet., Mayo Clin. **18**:199 (June 30) 1943. (*b*) Kaposi's Varicelliform Eruption, Arch. Dermat. & Syph. **50**:99 (Aug.) 1944.

4. Lynch, F. W.: Herpes Simplex as a Complication of Eczema, paper read at the meeting of the Ramsey County Medical Society, April 24, 1944.

5. Wenner, H. A.: Complications of Infantile Eczema Caused by the Virus of Herpes Simplex, Am. J. Dis. Child. **67**:247 (April) 1944.

Heys and Harrison [6] had demonstrated the presence of herpetic virus. In discussing Lynch's presentation [7] at the 1944 meeting of the American Medical Association, Ebert [8] reported that he had demonstrated inclusion bodies typical of the herpes group of diseases and had produced keratitis in a rabbit's eye. At about the same time Lane [9] discussed the subject before the American Dermatological Association and presented excellent photographic representation of several cases of the disorder.

The present report deals with 4 additional cases of extensive or disseminated herpetic eruptions, in but 1 of which the course and symptoms

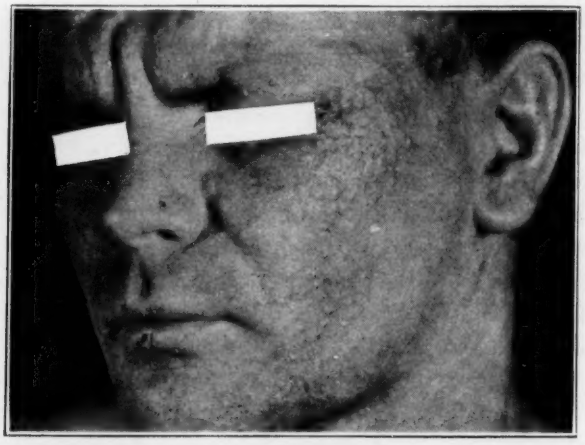

Fig. 1.—Kaposi's varicelliform eruption (case 5) with labial herpes simplex which preceded the extensive facial eruption.

were as severe as those usually associated with the condition in the title, Kaposi's varicelliform eruption.

CASE 5.—D. S. (fig. 1), a man aged 23 years, had had extensive eczema since birth. In recent years it had been present principally on the face, in the cubital areas and on the forearms and hands; at certain times it was dry, and at other times it was exudative.

On March 15 labial herpes simplex developed; on March 17 the eruption extended near the left eye, and it continued to spread until March 20, after which the eruption became severer but without development of additional lesions.

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6. Blattner, R. J.; Heys, F. M., and Harrison, M.: A Filterable Virus Isolated from a Case of Kaposi's Varicelliform Eruption, Science **99**:432 (May 26) 1944.

7. Lynch, F. W.: Kaposi's Varicelliform Eruption: Extensive Herpes Simplex as a Complication of Eczema, Arch. Dermat. & Syph. **51**:129 (Feb.) 1945.

8. Ebert, M. H., in discussion on Lynch.[7]

9. Lane, C. W., and Herold, W. C.: Kaposi's Varicelliform Eruption: Report of Five Cases, Arch. Dermat. & Syph. **50**:396 (Dec.) 1944.

Examination then revealed about fifty discrete tense vesicles on the right cheek; there were many similar lesions over the left zygoma and on the left cheek. The bases of the lesions were red, and the larger lesions were umbilicated. The left preauricular node and the right and left submaxillary nodes were enlarged. On March 22, the temperature was 99.8 F. and the lesions were regressing. On March 24 and 25 he had nausea, malaise, headache and some dizziness. In the next ten days the eruption gradually disappeared, without scar but leaving hyperpigmentation.

On March 20 fluid was obtained from a blister and inoculated on the cornea of a rabbit. At forty-eight hours severe keratoconjunctivitis had developed. After a week there developed in the rabbit paresis of the right legs and a tendency to walk in a circle, falling toward the affected side. On April 6, the rabbit was killed and sections of the brain were stained with hematoxylin and eosin. Scattered through the brain were found small areas of necrosis and round cell infiltration. In these areas the nerve cells showed margination of the nuclear chromatin, and intranuclear, acidophilic inclusion bodies were present.

The appearance and course in this case were characteristic of moderately severe examples of Kaposi's varicelliform eruption. In the 3 following cases, the eruption was much less extensive and the course was mild. In case 6 there were no signs or symptoms of toxicity. These cases are presented for the purpose of pointing out that while Kaposi's varicelliform eruption may be a clinical entity there are undoubtedly many cases in which herpetic eruptions are more extensive than ordinary herpes simplex but less extensive and severe than Kaposi's varicelliform eruption.

Case 6.—A. L., a woman aged 20 years, had suffered from extensive chronic eczema for about ten years. After the appearance of labial herpes simplex the new moist and papulovesicular eruption appeared, also in the form of grouped lesions on both upper lids, and subsequently spread on the chin at a distance from the labial eruption. New lesions continued to develop over a period of several days, without evidence of general toxicity. Recovery was prompt.

Case 7.—M. K., a patient with extensive facial acne, noted redness and swelling below each ear and burning and itching on the upper lip. On the following day the eruption spread over the face, and for several days the temperature rose to 100 F. When the patient was seen on the fifth day of her illness, the face presented an extensive eruption of single and grouped bright red papules, some papulovesicles and some crusted lesions. The patient felt generally ill. The throat was sore, and the left tonsil presented a few small discrete white areas. The white blood cell count was 6,700, and the sedimentation rate of the blood was 44 mm. in one hour. On the following day more of the papules transformed to vesicles, but the eruption improved steadily thereafter. The temperature was 99.4 F. and 99 F. the two succeeding days.

Case 8.—F. T. A., a man aged 69 years, stated that he had had several attacks of eczema over a period of ten years, but the current outbreak was said to be the severest. There were discrete tense vesicles, vesicopustules and crusted lesions, all with erythematous papular bases. They were in a group on the lateral portion of the left upper lid and eyebrow and were numerous near the left angle of the mouth. On the face they were scattered, more on the left side. There were

a small left preauricular node and a larger left submental node. His temperature was 99.6 F. He was vaccinated with smallpox vaccine, and the facial eruption was improved when he returned two days later but a few discrete, crusted papular lesions had appeared on the hands and ankles. The temperature was then 98 F. Subsequently the eruption healed rapidly, leaving areas of scaling and thickening on the lids, elsewhere on the face and on the neck and wrists, as before the acute eruption.

The report of Barton and Brunsting in 1944 provided a thorough review of previously published data regarding Kaposi's eruption. In the accompanying table we have summarized certain data concerning the recent cases in which herpetic infection has been proved or may reasonably be assumed (table). No important differences are apparent in a contrast of this group with the group reviewed by Barton and Brunsting in which the cause was unknown. This absence of difference suggests that herpetic infection may be the only cause of Kaposi's varicelliform eruption.

DIAGNOSIS

In contrast with the reports of laboratory studies by most other authors, the diagnosis of extensive herpes simplex was based on clinical observation in each of the 7 cases reported in our two series. Since the herpetic virus was found and identified in the 2 cases in which proper search was made, there is not much reason to doubt the diagnosis in any case. It is our belief that clinical diagnosis is not difficult if one thinks of the correct possibility. The observer must realize that herpes simplex exists in several forms, one of which is an extensive eruption superimposed on a preceding dermatosis, and that Kaposi's varicelliform eruption is not a particularly satisfactory descriptive term for this disease because not all patients (perhaps only a minority) present such extensive eruptions and general toxemia. Though there may be clinical resemblance to varicella in some cases, the resemblance can be slight and the vesicles can better be described as herpetic. In spite of the greater extent of Kaposi's varicelliform eruption, the diagnosis depends chiefly on recognition of the resemblance to herpes simplex. The inflammatory papules quickly become vesicles which are tense, and some of them are umbilicated. They soon rupture, perhaps because of the acuity of the inflammatory process but also because they are subjected to trauma because of the attempts to relieve the discomfort of the preceding eruption of which the herpetic infection is a complication. The grouping of lesions, so characteristic of herpes simplex, is less striking in this disease but is still evident to careful examination.

With any considerable extent the eruption is accompanied with general symptoms whose severity is greater than one would expect with pyogenic infection of similar extent. There is fever, loss of appetite, lassitude, malaise or even prostration. In the cases of severer condi-

Summary of Data in Reported Cases of Kaposi's Varicelliform Eruption

Author	Age of Patient	Sex	Severity	Virus Identified	Contact with Herpes	Herpes Labialis	Preceding Dermatitis
Esser	1. Infant	..	Severe *; died	In 2 cases †	Not stated; cases apparently epidemic	Not stated	Infantile eczema all cases
	2. Infant	..	Severe; recovery				
	3. Infant	..	Severe; recovery				
	4. Infant	..	Severe; recovery				
Barton-Brunsting	1. 30 yr.	M	Severe; meningeal symptoms	No	Not stated	No	Atopic eczema
	2. 21 yr.	F	Mild	Yes	Not stated	Yes	Atopic eczema
Wenner	1. 5 mo.	F	Died ‡	Yes	Not stated	Not stated	Infantile eczema
	2. 20 mo.	M	Severe; recovery	Yes	Not stated		Infantile eczema
	3. 8 mo.	F	Severe; recovery	Yes	Not stated		Infantile eczema
Lane and Herold	1. 20 yr.	M	Mild	No	Not stated	No	Neurodermatitis
	2. 14 yr.	M	Moderate	No	Not stated	No	Eczema
	3. 17 yr.	F	Moderate	No	Not stated	No	Neurodermatitis
	4. 3 yr.	F	Severe	No	Not stated	No	Neurodermatitis
	5. 15 mo.	..	Severe	Yes	Not stated	No	Eczematoid eruption
Lynch	1. 2½ yr.	M	Mild	No	Father	No	Atopic eczema
	2. 20 yr.	F	Moderate	No	No	Yes	Atopic eczema
	3. 10 mo.	M	Moderate	No	Mother	No	Infantile eczema
	4. 54 yr.	F	Mild	Yes	Possible	No	Atopic eczema
Ebert	1. "Young" woman	F	Severe	Yes	Not stated	No	Not stated
Lynch and Steves	5. 23 yr.	M	Moderate	Yes	No	Yes	Atopic eczema
	6. 20 yr.	F	No symptoms	No	No	Yes	Atopic eczema
	7. 28 yr.	F	Mild	No	No	No	Excoriated acne
	8. 69 yr.	M	Mild	No	No	No	Atopic eczema

* Report of autopsy suggested encephalitis.

† Seidenberg.[3]

‡ Encephalitis with herpetic virus isolated from brain of the infant.

tions one is likely to observe signs and symptoms of cerebral involvement. As in many diseases due to viruses the white blood cell count is elevated but not to the degree seen in pyogenic disorders. Neither the general symptoms nor the course of the eruption is greatly influenced by ordinary therapy, including the use of sulfonamide drugs. As with herpes simplex, the inflammation may be slightly relieved by proper topical therapy and the symptoms may be somewhat alleviated, but the eruption pursues a course of five to ten or twelve days, depending on its extent and severity.

The correct diagnosis may be aided somewhat by the history of a preexisting eruption having erosions or excoriations allowing inoculation and spread of the virus. The patient may have ordinary herpes simplex of the lips or eyelids, present for one to several days before the rapid extension of the inflammation. In other cases one may obtain a history of contact or even observe on the patient's attendant evidence of preceding localized herpes simplex.

It is possible that other than herpetic infections can be superimposed on eczematous eruptions producing eruptions like that of Kaposi's disease. It is possible that pyogenic infection can produce a similar eruption.[10] In attempting to confirm a diagnosis of herpetic complication of eczema, one is confronted with certain difficulties. Laboratory investigation of viruses is time consuming, and the facilities are not always or everywhere available. In order to get successful results, one must obtain fluid from an intact vesicle in the first several days of the illness, at a time when the patient may not yet have presented himself for examination. Inoculation of the cornea of a rabbit is the starting point for identification of the virus. However, as shown by Ebert, the inclusion bodies of herpes simplex may be found in histologic sections of the eruption.[8] The development of a keratoconjunctivitis may follow inoculation with viruses of both vaccinia and herpes simplex, making the demonstration of inclusion bodies essential. The diagnosis of herpetic infection is established by the appearance of the acidophilic intranuclear inclusion bodies of herpes simplex in the cornea during the first forty-eight hours or later in the brain. Immunologic studies are difficult and usually unnecessary, and the presence of antibodies against herpes simplex virus in human blood serum is subject to great variation.

It is our opinion that the demonstration of herpetic inclusion bodies, in the lesion itself, in the cornea of the rabbit soon after inoculation or in the brain after encephalitis develops, is the most expedient and reliable method of establishing a herpetic causation (figs. 2 and 3).

10. McLachlan, A. D., and Gillespie, M.: Kaposi's Varicelliform Eruption: Epidemic of Sixteen Cases, Brit. J. Dermat. **48**:337 (July) 1936.

Fig. 2.—Section from a rabbit's brain after the cornea was inoculated with herpetic virus. There are three areas of necrosis and cellular infiltration. It is in areas like this that one finds inclusion bodies such as are demonstrated in figure 3. × 90.

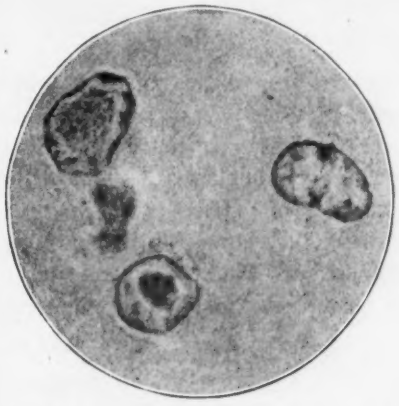

Fig. 3.—Drawing of changes observed in a single microscopic field from the brain of a rabbit whose cornea had been inoculated with herpetic virus. In the three neurons on the left are seen intranuclear herpetic inclusions in various stages of development. In the cell on the right there is margination of chromatin, which is a constant finding in herpetic infection.

EPIDEMIOLOGY

It has sometimes but not always been possible to determine the source of herpetic infection in Kaposi's varicelliform eruption. Esser reported a small epidemic, implying the presence of contagion from child to child, but it is possible that the source in each case may have been a nurse or other attendant suffering from herpetic infection. Such a method of inoculation was reported in cases 1 and 3 of the first series reported by Lynch.[7] In the first instance a child was exposed to his father, who had herpetic infection of the eyelid, and in the third case an infant was exposed to his mother, with labial herpes. In case 4 the source of infection may have been the attending physician. Apparently autogenous inoculation also occurs. Thus in case 6 of our present series and in case 2 previously reported, the onset of the varicelliform eruption was preceded for two days by labial herpes. In 1 case reported by Barton and Brunsting the extensive eruption was preceded by localized herpes simplex.[8] In discussing the paper by Lane and Herold, Lynch pointed out that the lantern slides of the photographs showed suggestive evidence that localized herpes simplex had occurred on the upper eyelid in cases 1 and 3, because lesions were further advanced and grouped more closely than elsewhere (see particularly figure 3 in their publication).[9]

TREATMENT

In ordinary cases of Kaposi's varicelliform eruption there is little to be done in addition to reasonable use of topical measures according to the usual dermatologic principles. In cases of severe eruption with progressive toxemia and evidence of involvement of the central nervous system, one should consider the use of serum therapy, as suggested by Evans, Bolin and Steves.[11]

TERMINOLOGY

Terminology deserves brief discussion in the light of both etiologic and clinical advances in recent years, which make possible a more satisfactory classification and nomenclature. In discussion of the suggested titles "eczema herpeticum" and "extensive herpes simplex complicating eczema (or other dermatoses)," Sulzberger suggested that the disease be spoken of as "disseminated herpes simplex" or "Kaposi's form of herpes simplex."[12] Kaposi himself suggested "eczema herpetiforme."[13] In a related disease, vaccinia, one speaks of multiple vac-

11. Evans, C. A.; Bolin, V. S., and Steves, R. J.: Kaposi's Varicelliform Eruption. Addendum: Experimental Data with Suggested Therapeutic Application, Arch. Dermat. & Syph. **51**:134 (Feb.) 1945.

12. Sulzberger, M. B., in discussion on Lynch.[7]

13. Kaposi, M.: Pathology and Treatment of Diseases of the Skin, ed. 4, translated by J. C. Johnston, New York, William Wood & Company, 1895, p. 346.

cinia in cases of less extensive eruptions, but when the eruption is more extensive, is superimposed on eczema and results in severe toxemia one uses the term "eczema vaccinatum." Similar wording in cases of herpetic infections would utilize the term "Kaposi's eczema herpeticum," mention of varicella being avoided, whose virus is not concerned in the disease.

If all eruptions can be called herpetic when caused by the virus of herpes simplex, there are then two main groups of cases; the first are those in which the virus exerts its influence on previously apparently intact skin. The eruptions may vary in site and extent but are clinically closely comparable. Herpes simplex may be (*a*) localized herpes

Fig. 4.—Herpes simplex which is more extensive than usual but still localized.

simplex (the site, i. e., labial, genital, aural or ocular being specified) or (*b*) extensive herpes simplex, in which the eruption is of greater than usual extent, presenting as a single group of lesions or with the addition of smaller groups or single lesions nearby.

Lutz [14] described 2 cases of this type of eruption, under the name "acute vacciniform or varioliform pustulosis." Figure 4 presents a somewhat comparable eruption but without satellite lesions. In Lutz's cases the vesicles were more widely distributed, though limited to the face, and the lesions were more discrete.

14. Lutz, W.: Ueber Pustulosis vacciniformis sive varioliformis acuta, Dermatologica **86**:138, 1942.

More extensive eruptions may follow the exposure of nonintact skin to herpetic virus. The extent of the eruption and the severity of the illness are chiefly dependent on the nature and extent of the preceding eruption and the age of the patient. The preceding eruption is not always eczema.

Herpetic inoculation as a complication of another dermatosis may be either (*a*) mild, but with the eruption usually of greater extent than in extensive herpes simplex (*b* in foregoing classification) and scattered in distribution, or (*b*) severe (Kaposi's varicelliform eruption, Kaposi's herpetiform eruption or eczema herpeticum).

SUMMARY

The purposes of this presentation have been two. First, we have reported an additional instance of the demonstration of the virus of herpes simplex in Kaposi's varicelliform eruption. Second, we have described several additional examples of disseminated herpetic infection occurring with clinical manifestations less severe than Kaposi's varicelliform eruption but severer and more extensive than those usually noted in herpes simplex (in the second classification presented). Whether or not one chooses to use these terms, it will be well to remember that there are variations in the clinical features of herpes simplex, from the mild disease characterized by several small papulovesicles to a severe, generalized eruption accompanied with systemic infection and possibly fatal termination.

DERMATOPHYTOSIS OF THE FACE CAUSED BY TRICHOPHYTON CAMEROUNENSE

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THE FOLLOWING case of dermatophytosis of the face seems worthy of publication, since the causative fungus presented features that rendered its detection difficult enough for one to assume that the true nature of similar cases may have been overlooked. The fungus involved, Trichophyton (Grubyella) camerounense (Ota and Gaillard 1926), has been recovered only once. It was found in the mycotic lesions of a bull transported from Cameroun, West Africa, to Paris, France, for studies in tropical piroplasmoses.[1] Unknown as yet has been its occurrence in America and its pathogenicity to human beings.

REPORT OF A CASE

A white boy, 14 years old, complained of red spots on his face that had appeared three months previously on the right cheek. They had spread to the neck and to the left eye and had been slightly itchy.

On examination, nearly the entire right cheek presented a red, round area that when seen from a distance seemed to be a healthy red cheek. At closer inspection, however, the red area as a whole was seen to be slightly elevated above the level of the normal skin. It was covered by a thin scaliness, comparable to chapped skin caused by rough weather. There was no clearing in the center. The border of the area was well defined but was in no way different from other portions of the lesion. A similar but smaller area, of oval shape, was seen on the skin covering the right lower rim of the mandible. A third lesion filled the left sulcus infrapalpebralis.

A scraping was taken from the border of the largest lesion. Microscopic specimens prepared with a solution of potassium hydroxide revealed only a few mycelial threads about 2 microns in diameter, which failed to show the sharply defined refraction rarely lacking in the hyphae of the genus Trichophyton. When stained with a 0.5 per cent solution of cotton blue C 4 in lacto-phenol, however, the specimen presented numerous, large, nearly round spores, measuring up to 14 microns in diameter (figure, *a*).

Glucose-peptone slants inoculated from the scraping developed several colonies of cocci. At the end of four weeks, there became visible three colonies, of pin-

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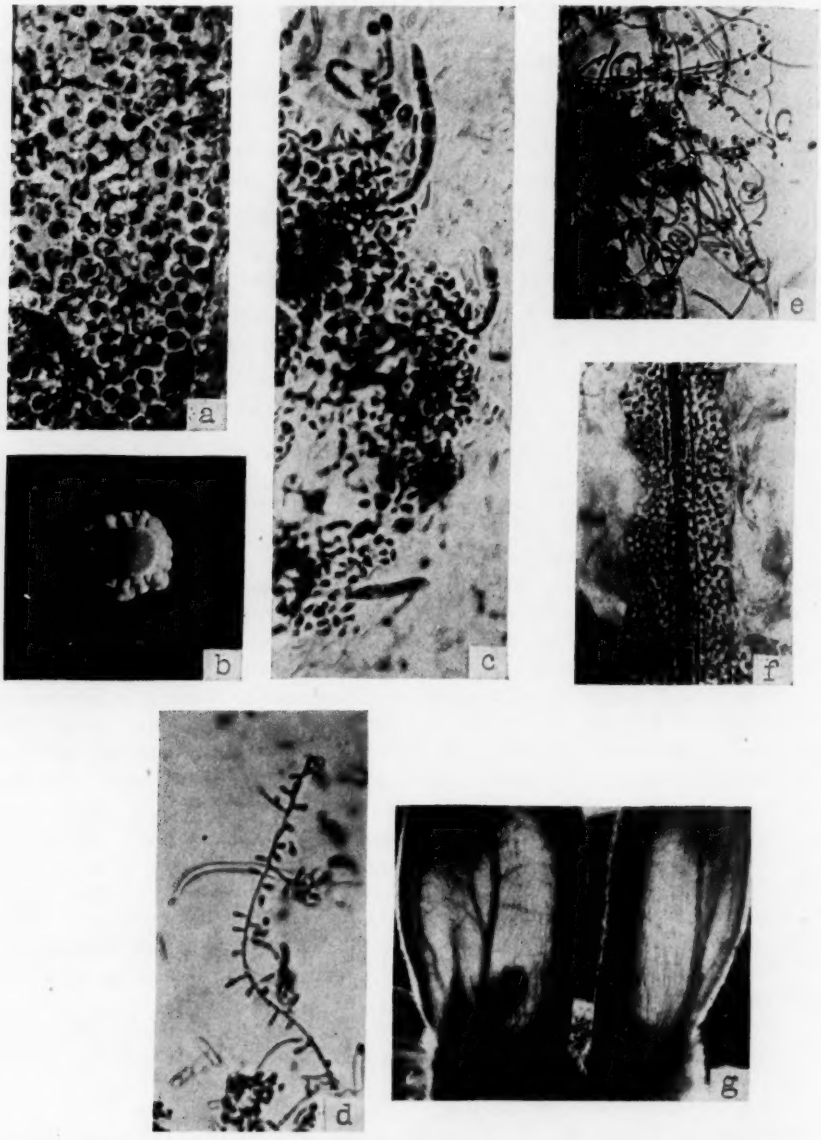
Dr. Bernhardt died Feb. 27, 1946.

From the Department of Dermatology and Syphilology (Dr. John Godwin Downing), Boston City Hospital.

1. Ota, M.: Sur une teigne trichophytique d'un bovidé du Cameroun produite par une espèce nouvelle de Grubyella, G. camerounensis N. Sp., Ann. de parasitol. **4**:14-21, 1926.

head size and shape, that were covered with a short, velvety aerial growth. Subcultures on peptone agar developed faster presenting an elevated, white, powdery center and irregular, colorless, submersed rays. On transfer to a medium composed of 2 per cent maltose, 8 per cent glucose and 1 per cent Fairchild peptone



(*a*) Chlamydospores in scraping from skin, (*b*) seven weeks' old subculture on test medium (1:1), (*c*) fuseaux from rice culture, (*d*) aleurosphore from corn meal agar, (*e*) spirals from corn meal agar, (*f*) rabbit hair surrounded by large spores, (*g*) lesion on left ear lobe of rabbit seven weeks after inoculation. (All microscopic specimens were stained with cotton blue in lacto-phenol).

agar, a hemispheric colony developed. This medium, when Weidman's researches [2] are taken into account, with available American ingredients resembles as closely as possible Sabouraud's original test medium. After four weeks at room temperature the hemisphere was 8 mm. in diameter and 4 mm. high and was covered with a slightly brownish, velvety growth. After another week it was surrounded with a ring, lighter in color, 3.5 mm. broad and 1.5 mm. high. This ring presented sixteen radial furrows between sectors that slanted to them and to their rounded peripheral ends. The center of the colony resembled the protruding disk of some flowers, such as certain asters, pyrethrums and chrysanthemums, and the surrounding sectors resembled the petals of these flowers. After two more weeks, a fluffy aerial growth appeared on two spots of the periphery (figure, *b*). This disappeared in the following weeks, however, being replaced by an irregular and more furrowed extension of the colony. Repeated subcultures on the same medium also developed hemispheres, which progressed, however, to approximate the shapes of Trichophytons, described as plicatile, papillose, verrucose and floriform, except for the difference in color, which was a shade of brown or, rarely, white.

Hanging block and hanging drop cultures in peptone, with or without maltose or glucose, present as main features pediculate and intercalary chlamydospores. Corkscrew-like hyphae were also seen in liquid medium. On rice medium there developed aleurospores (2 by 4 microns) on simple, rarely on compound, thyrsi, as well as fuseaux (up to 4 by 41 microns), with up to six compartments (figure, *c*), and chlamydospores. On corn meal agar there developed aleurospores, chlamydospores and spirals (figure, *d* and *e*). The wall of the hyphae as well as the wall of the chlamydospores failed to take the stain (cotton blue). Within the hyphae, well stained rectangular bodies were visible. As soon as chlamydospores became abundant, poorly stained filaments and unstained chlamydospores became numerous. Fuseau-like chlamydospores were occasionally seen, but fuseaux of the type seen in rice cultures were never observed to change to chlamydospores.

The original scraping was kept between slides at room temperature. Portions of it were inoculated on culture medium after several months. Primary colonies developed from a three month and a six month old inoculum. The colonies appeared in some instances after two weeks. Their shape on glucose-peptone agar was always hemispheric.

Animal Inoculations.—On the inoculated ear lobe of a rabbit there appeared after three weeks a scaly lesion, which changed during the following weeks to a crusty, elevated, round area (figure, *g*). Microscopically, the scales contained sporulated filaments. At the time the crusts formed, most of the hair follicles were filled with large spores (up to 4.5 microns in diameter), which surrounded the hairs (figure, *f*). Although numerous specimens were examined, not a single hair was found to be invaded by fungous elements. The lesion healed after seven weeks. The other ear lobe was then inoculated as well as the ear lobe of another rabbit, formerly inoculated with Trichophyton mentagrophytes, var. asteroides. Both inoculations developed in a similar manner to the lesion shown

2. (*a*) Weidman, F. D., and McMillan, T. M.: A Comparison of Ingredients of Ringworm Culture Mediums with Special Reference to American and French Crude Maltose, Arch. Dermat. & Syph. **4**:451-468 (Oct.) 1921. (*b*) Weidman, F. D., and Spring, D.: A Comparison of Ringworm Culture Ingredients, ibid. **18**:829-851 (Dec.) 1928.

in the figure, *g*. A guinea pig that was inoculated died of an unknown cause after sixteen days; sections of the skin showed hyphae invading the hair follicle. The same kind of fungus was recovered by culture from the scales and crusts of every animal inoculated.

Etiology.—The patient frequented a railroad yard to play with cattle that were fenced in there before being taken to the slaughterhouse. The patient's sisters, who did not visit the cattle yard, did not become infected.

Therapy.—The first treatment consisted of the application of ointment of benzoic and salicylic acid prepared with Aquaphor. This ointment proved irritating to the eye, and the lesion near it was therefore treated with an ointment containing 1 per cent yellow mercuric oxide. It improved faster than the other lesions, which were then treated with diluted tincture of iodine. Improvement remained incomplete until all the lesions were treated with 2 per cent yellow mercuric oxide in Aquaphor. Thereafter they cleared up rapidly.

COMMENT

Tinea circinata is a term designating ringlike lesions. Since there was no central clearing in this case, the term dermatophytosis seems more appropriate.

The true nature of the disease might have been overlooked by routine methods, since there were only a few indistinct mycelial filaments to be found, not to mention the slow development and smallness of the colonies on culture medium. The irregular mass of chlamydospores in the native specimen could not be distinguished from other cell material until it had been stained. The development of colonies of cocci on the routine slants rendered improbable the later appearance of fungous colonies, the nature of which became visible only on scrupulous inspection.

Microscopic examination of mounts from different mediums revealing aleurospores, fuseaux and spirals establishes the fungus involved as a Trichophyton. The spores surrounding the hair identify it as an ectothrix. Their large size justifies the classification as a megaspore. Sabouraud reported three species of faviform fungi among the megasporic Ectotrichophytons. The fungus described in this paper resembles these species so far as its colonies are slow growing, covered only with a minute velvet and showing nearly exclusively chlamydospores when grown on Sabouraud's medium. The hemispheric form of the colony up to four weeks is the main difference, if one does not consider the large number of chlamydospores in the cutaneous scraping and the aleurospores, fuseaux and spirals revealed on mediums that were hoped for but not used by Sabouraud.[3] A review of the literature failed to reveal a fungus with exactly the same description. There is only one Trichophyton presenting similarities enough to assume that it belongs to the same species. It is Grubyella camerounensis (Ota and Galliard,

3. Sabouraud, R.: Les teignes, Paris, Masson & Cie, 1910, p. 652.

1926), renamed Trichophyton papillosum by Lebasque in 1933 [4] and Favotrichophyton camerounense by Dodge.[5] There is the same small size of the colony on a medium containing glucose and peptone, the same hemispheric shape of the early colony, later on sometimes surrounded by a folded periphery, and the same prevalence of chlamydospores on Sabouraud's medium. The differences are not striking enough to justify establishment of a new species, although the name Trichophyton hemisphericum seems more appropriate in view of the shape of the early colony on a medium containing glucose or maltose.

The inoculations of animals show that the fungus is pathogenic, at least to rabbits and guinea pigs. The slow development of the experimental lesions and their long persistence are in contrast to results of inoculations with most of the trichophytins, as the resulting lesions usually appear during the second week and vanish during the third week.

SUMMARY

An unusual mycosis of the face and its causative organism, Favotrichophyton camerounense, are described. This is the second isolation of this fungus, the first one in America and the first from a human lesion. Difficulties in its detection are mentioned. An ointment containing 2 per cent yellow mercuric oxide in Aquaphor seems to be curative.

4. Lebasque, J.: Les champignons des teignes du cheval et des bovidés, Thesis, University of Paris, 1933, pp. 71-77.

5. Dodge, C. W.: Medical Mycology, St. Louis, C. V. Mosby Company, 1935, pp. 515-517.

GRANULOMA INGUINALE INVOLVING BUTTOCK AND LYMPH NODE

Cultivation of the Donovan Body in Embryonic Yolk

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LIEUTENANT COLONEL ELSON B. HELWIG

AND

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MEDICAL CORPS, ARMY OF THE UNITED STATES

THE FOLLOWING instance of granuloma inguinale is reported because of the unusual clinical history, involvement of the lymphatic system and establishment of the etiologic agent by means of cultivation in embryonated eggs.

REPORT OF A CASE

Clinical Course.—A 20 year old Negro was admitted Jan. 6, 1945, complaining of a "sore near my rectum." Approximately four weeks before admission he first noted a painful pimple on his left buttock. It rapidly increased in size so that within three days he was unable to continue his work as a checker of cargo that was being unloaded on the beaches of Leyte, Philippine Islands. The pimple ruptured on the fourth day and drained a considerable amount of pus, which relieved the pain. Copious amounts of pus drained during the ensuing week, the lesion increased in size, and he was admitted to a station hospital. There with the patient under pentothal sodium anesthesia an incision was made, with the release of a considerable amount of pus. A diagnosis of ischiorectal abscess was made, and two weeks later he was transferred to another station hospital, because the lesion was increasing in size, tender, indurated and had a foul discharge. He was later transferred to this general hospital for further treatment.

The previous history of this patient is of interest in that he was admitted to a general hospital Feb. 10, 1944, almost one year before this admission, because he was allegedly involved in homosexual practices, notably sodomy. Examination, including rectal smears, revealed no abnormality, and repeated questioning failed to elicit a confirming admission from the patient. The history further indicated that after discharge from the hospital he was the only one of several men in his unit who was not declared guilty of homosexual practices by a General Court Martial.

He admitted frequently visiting houses of prostitution in Honolulu, Territory of Hawaii, during the summer of 1944 but stated that he definitely did not have sexual contact after September, when he sailed for Leyte. The patient stated that he had never had a lesion on his penis.

Examination of this asthenic and acutely ill Negro revealed nothing remarkable except that on the left buttock adjacent to the anal orifice, in the 9 o'clock position, there was an indurated and undermined area about 5 cm. in diameter containing

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several fistulas that drained a foul purulent fluid and necrotic tissue. A similar area about 2 cm. in diameter was seen in the 11 o'clock position. Surrounding these areas for a distance of 2 to 4 cm. there was a moderately tender zone of induration. On the right buttock in the 2 o'clock position there was an area of induration about 5 cm. in diameter with three tiny fistulas near its anal margin. There was no lesion on the genitals. The inguinal lymph nodes were not enlarged or tender.

On admission the patient's immediate difficulty was interpreted as being due to an incompletely drained abscess. Incision and drainage were done Jan. 6, 1945, and biopsy specimens taken. It was found that immediately beneath the areas noted on the left buttock, the partially necrotic skin was entirely undermined by sloughing necrotic subcutaneous tissue. The sinuses of the two areas noted on the left buttock converged subcutaneously and led into an abscess cavity along the right side of the anus and rectum which was about 11 cm. deep and contained thick creamy pus. No pustules or sinuses were demonstrated to extend into the area of induration that surrounded this abscess cavity.

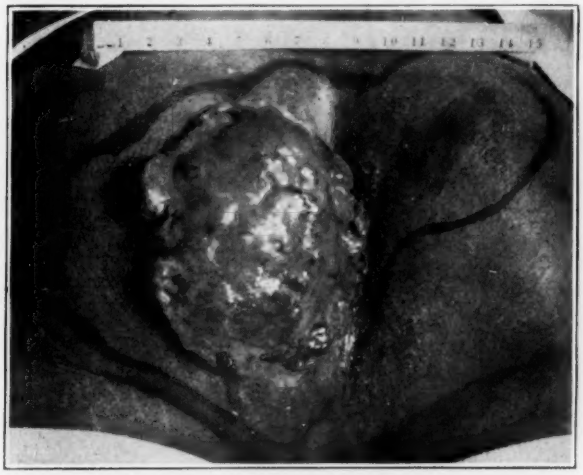

Fig. 1.—Appearance of lesions on Feb. 9, 1945, before treatment with fuadin. Dark line indicates the area of induration.

The patient was given penicillin, 25,000 units every three hours, and hot compresses. The drainage gradually decreased and became less foul and purulent. The necrotic tissue sloughed away, including the bridge of skin between the two lesions of the left buttock. During a period of three weeks the appearance of the lesion became different from that found on admission. It suggested a granulomatous process composed of spongy red moist granulation tissue. The advancing elevated, well defined, serpiginous border tended to roll over on the bordering skin (fig. 1). Also during this period a lymph node in the right inguinal region became definitely enlarged, but it was not tender.

The smear and culture taken on admission were negative. The biopsy showed acute and chronic inflammation with epithelial hyperplasia. The diagnosis was in doubt, so on January 29 the enlarged right inguinal lymph node was excised. Further biopsies and smears were taken of the lesion on the left buttock. The

report from these smears and biopsies established a diagnosis of granuloma inguinale.

On February 14 the first course of fuadin (sodium antimony III bis-catechol-2, 4 disulfonate) was started. The initial dose was 1.5 cc., followed in two days by 3.5 cc., and thereafter 5 cc. was given twice weekly for a total of 45 cc. A second course of fuadin was started on March 17. A third course was started on April 24, and the dosage increased to 5 cc. of fuadin every other day. At no time were toxic symptoms observed.

During this course of treatment with fuadin there was a gradual and definite improvement of the lesion. The foul discharge almost ceased, and the surface became covered with clean firm granulation tissue. The edges became level with the adjacent skin, and definite epithelization of the edges that was almost free of pigmentation was seen. The area of induration had decreased approximately 60 per cent (fig. 2). After three weeks of treatment the patient ceased to be bedridden, and thereafter he showed great improvement. On May 4 he was placed on orders for evacuation to the mainland.

Fig. 2.—Appearance of lesion on April 23, 1945, after treatment with 90 cc. of fuadin.

The blood cell count on admission January 6, was 3,670,000 red blood cells, hemoglobin 75 per cent, white blood cells 19,950, with 78 per cent neutrophils, 20 per cent lymphocytes and 2 per cent monocytes. Numerous blood counts during his stay in this hospital showed a gradual decrease in the white blood cell count and an increase in red blood cell count. On April 9 the blood cell count was 4,390,000 red blood cells, hemoglobin, 90 per cent, white blood cells 7,300, with 38 per cent lymphocytes, 59 per cent neutrophils and 3 per cent eosinophils. The sedimentation rate (determined by the Westergren method) dropped progressively from 108 mm. per hour on February 3 to 54 mm. per hour on April 29. The blood chemistry report on February 9 showed a total protein of 7.2 Gm., albumin 3.8 Gm. and globulin 3.4 Gm., giving an albumin-globulin ratio of 1:1. The formaldehyde-gel test showed a semigel in three hours. Repeated blood chemical determinations on February 26 and on April 9 showed no appreciable variation from these figures. Cultures taken January 6, January 22, January 23 and February 5

from the lesion on the buttock showed no growth, but one taken on February 2 showed scattered colonies of diphtheroids. Smears done on January 6 and February 2 showed no organisms, but on February 6 a smear demonstrated the presence of Donovan bodies. The Kahn and Wassermann reactions were negative on January 6, February 7, February 9 and April 26. On examination of the feces on February 8 and February 16, no occult blood, parasites or ova were found. Reactions to Frei tests on February 6 and February 12 were negative. Complement fixations with a lymphogranuloma venereum antigen on February 9 and April 26 both showed a reaction of 4 plus with an initial dilution of serum of 1:20.

Pathologic Examination.—One part of the gross specimen consisted of two masses of tissue measuring 3.4 by 1.3 by 1.2 cm. and 1.5 by 1 by 0.9 cm. Each mass of tissue was partially covered with dark skin. Along one margin the

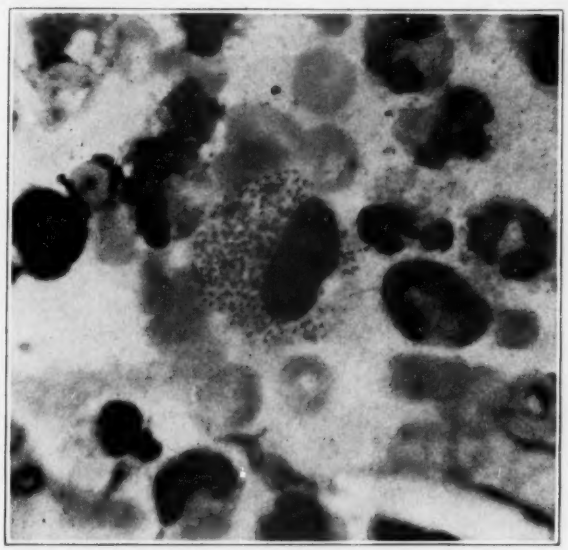

Fig. 3.—Mononuclear cell with intracellular Donovan bodies. Touch smear of ulcer of patient. Wright's stain; × 1,200.

skin was rolled and pale. The contiguous surface was ulcerated, irregularly granular and mottled red and yellow. The cut surface beneath the intact skin appeared as gray normal subcutaneous tissue. Beneath the ulcerated zone the cut surface was slightly translucent and gray-yellow with scattered hemorrhagic foci.

The second part of the specimen consisted of a lobular mass of tissue measuring 3.5 by 2.7 by 2.5 cm. The external surface was gray-pink with adherent bits of fibrous tissue. The cut section disclosed the outlines of two lymph nodes, the surface of which was gray-pink, congested and marked by small gray opaque foci.

The tissues were fixed in a solution of 10 per cent formaldehyde. Paraffin sections were prepared and stained with hematoxylin and eosin stains and Giemsa stain and by the silver impregnation method of Dieterle. In addition, touch smears were prepared from the tissue at the site of the ulcer and stained with Giemsa stain and with Wright's stain.

The cellular content of the touch smears was comprised predominantly of leukocytes but included many large mononuclear cells. The mononuclear cells generally contained many Donovan micro-organisms, which were frequently bacillary in shape with bipolar concentrations of chromatin and a well defined capsule (fig. 3).

For microscopic examination sections of tissue were selected to include the intact skin and the ulcerated zone. In general, all except the superficial layers of the skin contained pigment. There was a slight hyperkeratosis, and the rete pegs were frequently elongated and sometimes branching. The cutis showed edema of the interpapillary and subpapillary zones. Blood vessels and the skin appendages were surrounded by tenuous edematous stroma, and the perivascular stroma was infiltrated with inflammatory cells which were mostly plasma cells. There were several mast cells scattered throughout the stroma and near blood vessels. At the margin of the ulceration, slightly pigmented squamous epithelium extended irregularly into the underlying stroma.

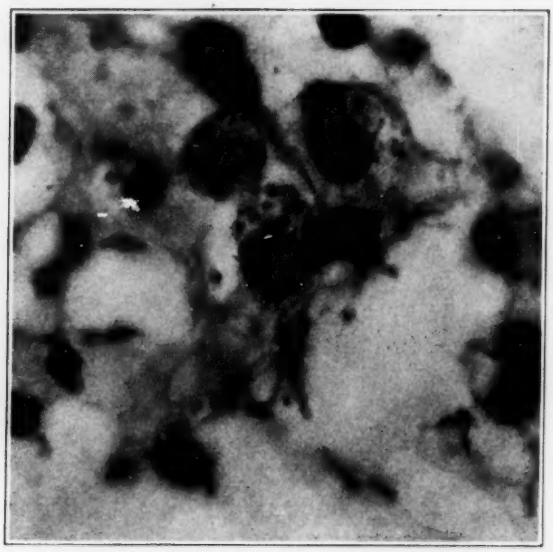

Fig. 4.—Mononuclear cells with intracellular Donovan bodies and vacuolated cytoplasm. Histologic section of ulcer of patient. Hematoxylin and eosin; × 1,500.

The base of the ulceration was composed of a luxuriant richly vascularized granulation tissue. The stroma between the capillaries was scanty, edematous and highly infiltrated with inflammatory cells and scattered collections of red blood cells. The exudate was often rich in polymorphonuclear leukocytes. In addition, there were lymphocytes, plasma cells and a number of mononuclear cells, particularly in the superficial zone, filled with minute bacillary bodies. In some instances the bacillary forms were situated in a vacuolated cytoplasm, and occasionally they were encountered outside of the cell (fig. 4).

On microscopic examination the general architecture of the lymph node was intact. There were a few small foci of fibrosis. The primary and secondary nodules were moderately prominent. The blood vessels throughout the node were dilated and hyperemic. Likewise, the peripheral lymph sinuses and to a slightly

lesser degree the central sinuses were dilated. The peripheral sinuses were often filled with lymphocytes, plasma cells, monocytes and a few polymorphonuclear leukocytes. Situated within the lymph sinuses were rare mononuclear cells containing minute bacillary bodies (fig. 5). The capsule in places was thickened by fibroblastic proliferation accompanied by a moderately heavy infiltration of cells, chiefly plasma cells and lymphocytes (fig. 6). Occasionally mast cells were encountered in the capsule and within the node.

Experiments.—On February 9 and again on February 15, specimens for biopsy were taken near the skin margin, and saline suspensions of the ground granulation tissue were inoculated into the yolks of embryonic chicks. On both occasions, an organism was isolated which resembled Donovania granulomatis as described by Anderson, De Monbreun and Goodpasture,[1] and on both occasions a passage strain was established.

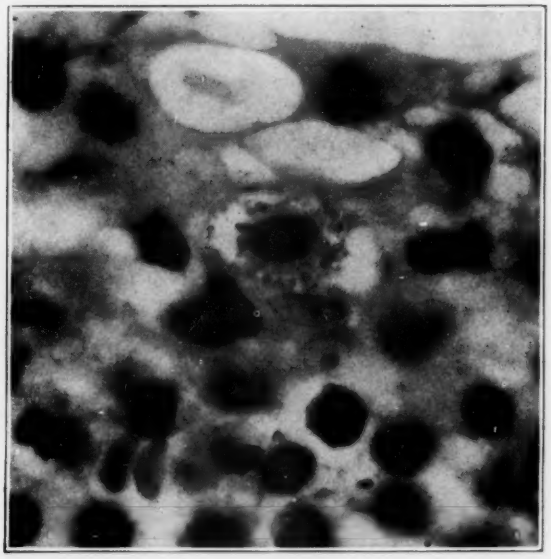

Fig. 5.—Mononuclear cell with intracellular Donovan bodies and vacuolated cytoplasm. Histologic section of inguinal lymph node. Hematoxylin and eosin; × 1,500.

The only difficulty encountered was the elimination of the few contaminating bacteria. Plate cultures of bits of tissue showed that the chief contaminants were Corynebacterium xerose and paracolon bacilli. Because the Donovan bodies were present in far greater number than the contaminants, it was possible to isolate the former by injecting the yolks of chick embryos with a series of tissue dilutions.

In one experiment, serial tenfold dilutions in sterile saline solution were made, beginning with ground granulation tissue. As all dilutions were made with the same pipet, they were crudely approximate. Of each dilution 0.1 cc. was inoculated

1. Anderson, K.; DeMonbreun, W. A., and Goodpasture, E. W.: An Etiologic Consideration of Donovania Granulomatis Cultivated from Granuloma Inguinale (Three Cases) in Embryonic Yolk, J. Exper. Med. **81**: 25 (Jan.) 1945.

into the yolk of a five day old chick embryo. Results are presented in the table. There it may be seen that the embryos inoculated with 10^{-3} and 10^{-4} dilutions, respectively, died within two or three days and had diphtheroids in their yolks; wheras embryos inoculated with dilutions of 10^{-6}, 10^{-7} and 10^{-8}, respectively, survived to harvest and showed only Donovania. No organisms were found in the yolk which had been inoculated with the 10^{-5} dilution. Presumably the diphtheroids had been diluted out of the inoculum. On the other hand, this embryo, which had been harvested seven days after inoculation, might have shown Donovania had it been harvested eleven days after inoculation, as were the positive embryos.

The two strains have been carried through twenty-eight and thirty passages, respectively, in embryonic yolk. The organism has shown many resemblances to those described by others. It has been a highly pleomorphic, gram-negative rod. In Wright stains it was often intensely bipolar, and "safety pin" forms were common (fig. 7). Some forms were indistinguishable from the Donovan bodies seen in touch smears made directly from the ulcer on the patient. It was frequently encapsulated. Several tests for motility were negative. In harvested yolk kept at room temperature (20—30 C.), the organisms have remained viable for four weeks, but not for ten weeks.

Isolation of Donovania Granulomatis

Chick Embryo	Dilution of Tissue in Inoculum *	Fate of Chick	Time of Harvest; Days After Inoculation	Stained Smears of Yolk †
IB 7	10^{-3}	Died in 3 days	7	Diphtheroids
IB 8	10^{-4}	Died in 2 days	7	Diphtheroids
IB 9	10^{-5}	Alive at harvest	7	No organisms
IB 10	10^{-6}	Alive at harvest	11	Donovania
IB 11	10^{-7}	Alive at harvest	11	Donovania
IB 12	10^{-8}	Alive at harvest	11	Donovania

* In each case 0.1 cc. of tissue dilution was inoculated into the yolk of a five day old chick embryo.

† Gram-stained and Wright-stained smears were examined.

Routinely, the inoculum used for passage was plated on blood agar, but the organism has never been observed to grow thereon. Blood agar, Loeffler's slants, thioglycolate broth, and infusion of beef heart containing 2 per cent horse serum failed to support growth, whether incubation was carried out in air, under 10 per cent carbon dioxide or anaerobically. On five occasions, the yolks of 2 infertile eggs have been inoculated in parallel with embryonated eggs. Regularly, the embryonated eggs supported growth, but the infertile eggs did not. In similarly arranged tests it was found that the organism was not propagated on the chorioallantoic membrane of the chick. In 6 chicks, it was found that the organisms dropped on the chorioallantoic membrane did not succeed in invading the chick and settling in the yolk, which would have offered a favorable medium for growth. Paraffin sections of the yolk stained with hematoxylin and eosin exhibited bodies morphologically similar to Donovan bodies within the yolk sac cells in 3 out of 4 embryos (fig. 8).

A heat-killed "bacterial" antigen prepared from seventh passage yolk cultures was injected intracutaneously in the forearm of the patient. An area of erythema and slight induration, 12 mm. in diameter, was apparent in twenty-four hours. A control site into which was injected ten times as much yolk material from uninoculated eggs showed no reaction. A subsequent test with ten times as much

antigen gave a twenty-four hour reaction that was 20 by 25 mm. but not as intensely red as the preceding one.

A "bacterial" antigen for complement fixation tests was prepared from infected yolk (twenty-ninth passage) by three cycles of differential centrifugation in plugged 50 cc. centrifuge tubes. In the first phase of each cycle the material was spun in a size 1 International centrifuge at 3,000 revolutions per minute for one hour, and the supernatant material was discarded. The precipitate was then suspended in a volume of sterile saline solution equal to the original volume

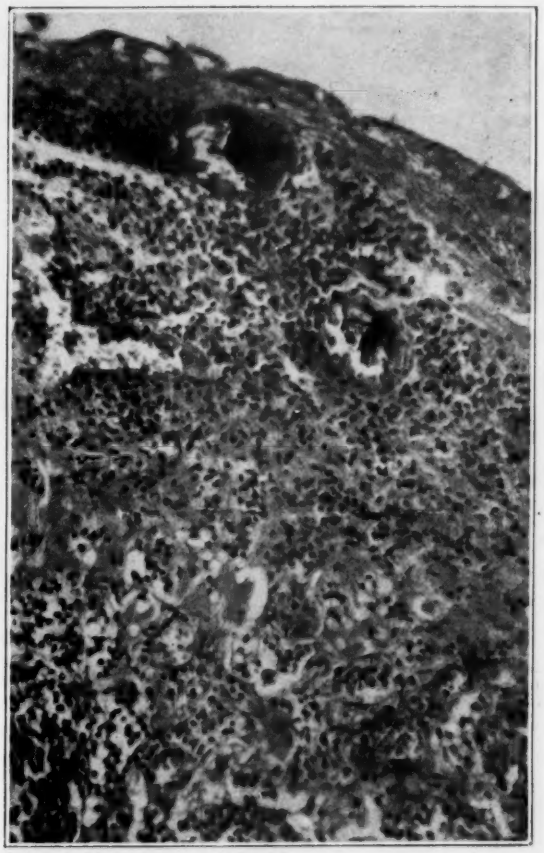

Fig. 6.—Inguinal lymph node showing infiltration of inflammatory cells in capsule and dilatation of lymph sinuses. Hematoxylin and eosin; × 105.

of yolk. In the second phase of each cycle the resuspended precipitate was centrifuged at 600 revolutions per minute for fifteen minutes, and the sediment was discarded. The final supernatant material was diluted 1:4 and used as the antigen, without further treatment. A Gram stain confirmed the presence of the organisms. A control antigen was similarly prepared, beginning with yolk taken from uninoculated embryos of the same age as the infected ones. The control antigen was used undiluted, but was only slightly more turbid than the diluted

"bacterial" antigen. Neither the "bacterial" nor the control antigen was anticomplementary.

For quantitative complement fixation tests, serial twofold dilutions of serums were prepared, and 0.2 cc. of serum or of serum dilution was used in each tube. Parallel tests were run with "bacterial" antigen and control antigen. Other-

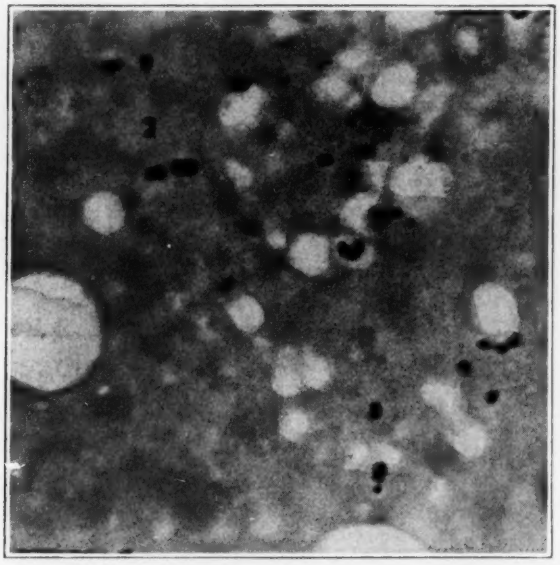

Fig. 7.—Smear showing Donovan bodies grown in embryonic yolk, ninth passage. Wright's stain; × 1,500.

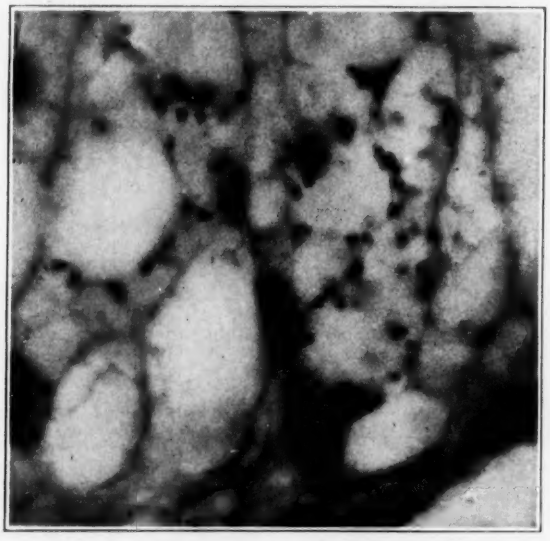

Fig. 8.—Histologic section of yolk sac epithelium of chick embryo with intracellular Donovan bodies, fifteenth passage. Hematoxylin and eosin; × 1,800.

wise, the tests were performed as in the Kolmer simplified complement fixation test for syphilis.

Serums had been collected from the patient on February 9 and April 26 and had been stored frozen. These were tested in the same run with serums from 20 normal persons which had been stored frozen. Both serums from the patient showed reactions of 4 plus in the lower dilutions, and reactions of 2 plus with an initial serum dilution of 1:64. In this series of tests nineteen of the twenty normal serums were negative; but one serum gave a reaction of 2 plus at an initial dilution of 1:2. In tests with two similar antigen preparations, weak reactions occurred with two other normal serums; however, the strongest reaction encountered with normal serum is that which has been reported. The second serum from the patient was slightly anticomplementary in the absence of antigen, and gave a plus-minus reaction with the control antigen at an initial serum dilution of 1:2. No other positive reactions with the control antigen were observed. It may be noted that ice box fixation was employed and the antigen had not been subjected to chemical treatment, two circumstances calculated to emphasize any tendency of the antigen to react with normal serums.[2] Nevertheless, the results clearly indicate a specific relationship between the paitent's serum and the organism isolated from him.

COMMENT

Granuloma inguinale is a chronic disease believed to be acquired during sexual intercourse. Many authorities consider the incubation period to be twenty to sixty days. It is much more prevalent in the Negro race than the white race.

The initial lesion is a papule or vesicle the surface of which becomes eroded, leaving a granulomatous ulcer. The usual concept of the characteristic fully developed lesion is that it has a base of soft beefy red granulation tissue that bleeds easily if traumatized and has sharply defined irregular serpiginous borders that are elevated and tend to roll over on the bordering skin. There is no pain unless gross secondary infection exists.

It is interesting to note that the lesion in the present case did not initially present the typical appearance of a granulomatous lesion. Instead it was somewhat painful, and there was a considerable amount of suppuration with undermining of the skin edges and the formation of a large abscess cavity adjacent to the wall of the anus and rectum. This has been mentioned only occasionally in the literature, by Pariser and Beerman,[3] D'Aunoy and von Haam,[4] and Sobel and Pensky,[5] and caused delay in establishing the diagnosis in our case.

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2. Wertman, K.: Nonspecific Complement-Fixing Antigen in Embryonic Egg Tissues, J. Lab. & Clin. Med. **30**:112 (Feb.) 1945.

3. Pariser, H., and Beerman, H.: Granuloma Inguinale, Am. J. M. Sc. **208**:547 (Oct.) 1944.

4. D'Aunoy, R., and von Haam, E.: Granuloma Inguinale, Am. J. Trop. Med. **17**:747 (Sept.) 1937.

(Footnotes continued on next page)

The definite enlargement of a lymph node in the right inguinal region, starting approximately one month after the onset of the original lesion, is of interest. It is generally accepted that granuloma inguinale is a disease of the skin and corium and not of the lymphatics. Strong [6] denies that the lymphatic nodes are affected, and Fox [7] points out that the neighboring lymphatic nodes are not enlarged. However, Greenblatt, Dienst, Pund and Torpin [8] were impressed by the frequency with which the inguinal lesion was preceded by a primary focus on the genitalia. In experimental production of the disease in human beings they were able to demonstrate Donovan bodies in underlying lymph nodes. They suggested that the Donovan bodies spread by way of the lymphatic system to the lymph nodes, where temporary, though mild, reactions with perilymphadenitis occur. They stated their belief that if the Donovan bodies reach the papillae and corium of the overlying skin during this process a subcutaneous granuloma is formed. Anderson, DeMonbreun and Goodpasture [1] aspirated material rich in Donovan bodies from two unruptured lesions in a Negro man with other ulcerative lesions of granuloma inguinale. Sobel and Pensky [5] reported a case in which there was bilateral inguinal adenitis, and along the lymph vessels of the dorsum of the penis two fluctuant abscesses proved to be due to the etiologic agent of granuloma inguinale.

According to Pund and Greenblatt,[9] there is a uniform histologic picture in pure or unmixed cases of granuloma inguinale. These authors have described the essential features consisting of (*a*) a massive cellular reaction in which luxuriant granulation is surcharged with plasma cells, (*b*) relatively few lymphocytes, (*c*) a diffuse sprinkling of polymorphonuclear leukocytes with focal collections in the superficies and papillae, (*d*) a pronounced marginal epithelial proliferation simulating early epitheliomatous changes and (*e*) pathognomonic large mononuclear cells within the granulation tissue. They stated their belief that the cytologic character of the large mononuclear cell together with its contained inclusion bodies permits the histologic diagnosis of granuloma inguinale to be made.

In 1939, Greenblatt, Dienst, Pund and Torpin [8] reported in 2 patients, 1 of whom had extragenital involvement, the presence of Donovan bodies, in the underlying cervical and inguinal lymph nodes of one and in one

5. Sobel, N., and Pensky, N.: Bubonulus in Granuloma Inguinale, Arch. Dermat. & Syph. **48**:494 (Nov.) 1943.

6. Strong, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, ed. 6, Philadelphia, The Blakiston Company, 1942.

7. Fox, H.: Granuloma Inguinale, J. A. M. A. **87**:1785 (Nov. 27) 1926.

8. Greenblatt, R. B.; Dienst, R. B.; Pund, E. R., and Torpin, R.: Granuloma Inguinale, J. A. M. A. **113**:1109 (Sept.) 1939.

9. Pund, E. R., and Greenblatt, R. B.: Specific Histology of Granuloma Inguinale, Arch. Path. **23**:224 (Feb.) 1937.

regional inguinal node in the other. In 1 other patient in whom the disease occurred spontaneously and in 1 patient in whom the disease was induced experimentally by inoculation of aspirated pus in the groins, the excised lymph nodes exhibited endothelial hyperplasia but no Donovan bodies. In one of the instances in which Donovan bodies were found the lymph node showed foci of suppuration. Two adjacent nodes showed only perilymphadenitis and lymphocytic infiltration of the capsule. In the present case the lymph node showed a decided but not uniform perilymphadenitis with both lymphocytes and plasma cells infiltrating the capsule. Although no definite abscesses were present in the node, the peripheral sinuses did contain a scattering of polymorphonuclear leukocytes as well as several mononuclear cells, plasma cells and lymphocytes. In addition, Donovan bodies were demonstrated in a few of the mononuclear cells. The present case, therefore, supports the concept that one of the routes of spread of granuloma inguinale is through the lymphatics. One can only speculate as to whether a lesion of the skin would have developed in the inguinal region in this patient. Unfortunately no culture studies were made of this enlarged lymph node.

It is well known that Donovan bodies do not grow on ordinary bacteriologic mediums. However, Anderson, DeMonbreun and Goodpasture [1] have described the cultivation of three strains in embryonic yolk. Cultivation of a fourth strain in embryonic yolk has been described by Sheldon, Thebaut, Heyman and Wall.[10] The Donovan organism has also been isolated and propagated by continuous tissue culture (by George O. Gey, as reported by Lyford, Scott and Johnson [11]). Anderson and his co-workers [12] have presented evidence for the etiologic relationship of their cultivated organisms to the disease granuloma inguinale, and have proposed the name "Donovania granulomatis" for the Donovan micro-organism, which they consider to be a bacterium with fastidious growth requirements. In its source, appearance, staining properties and biologic behavior, the present organism shows sufficient similarity to those of Anderson and his co-workers to justify its identification as Donovania granulomatis. Profuse growth in embryonic yolk and invasion of the yolk sac cells, as contrasted with failure to grow in the yolk of an infertile egg or on the chorioallantoic membrane have been noted by Anderson and his colleagues, who have also described skin tests with

10. Sheldon, W. H.; Thebaut, B. R.; Heyman, A., and Wall, M. J.: Osteomyelitis Caused by Granuloma Inguinale, Am. J. M. Sc. **210**:237 (Aug.) 1945.

11. Lyford, J., III; Scott, R. B., and Johnson, R. W., Jr.: Polyarticular Arthritis and Osteomyelitis Due to Granuloma Inguinale, Am. J. Syph., Gonor. & Ven. Dis. **28**:588, 1944.

12. Anderson, K.; Goodpasture, E. W., and DeMonbreun, W. A.: Immunologic Relationship of Donovania Granulomatis to Granuloma Inguinale, J. Exper. Med. **81**:41 (Jan.) 1945. Anderson, DeMonbreun and Goodpasture.[1]

heat-killed "bacterial" antigen. The cutaneous reactions of the present patient were qualitatively similar but less extensive.

The complement-fixing antigen herein described differed from that of Anderson and his colleagues in that it was composed largely of washed organisms, whereas that of Anderson and his colleagues was mainly ether-extracted, reprecipitated "capsular substance." However, the present antigen in all likelihood contained "capsular substance" along with the organisms. Although it was good enough to demonstrate a specific relationship between the patient's serum and the organism isolated from him, it would undoubtedly require modification and standardization before use as a serodiagnostic agent.

The fixation of complement by the patient's serum with a lymphogranuloma venereum antigen was of dubious significance in view of the negative reactions to the Frei tests obtained for the patient and the well recognized tendency of the antigen to give reactions which are not specific for lymphogranuloma venereum.[13]

SUMMARY

In a case of granuloma inguinale involving the buttock, perianal tissue and an inguinal lymph node, the onset as an acute suppurative process was atypical.

The diagnosis was established by: (*a*) the clinical appearance, (*b*) demonstration of Donovan bodies in the tissue and (*c*) response to specific treatment with fuadin.

The probable etiologic organism, Donovania granulomatis, was cultivated in embryonic yolk. The reactivity of the patient to the cultivated organism was demonstrated by positive reactions to intracutaneous and complement fixation tests.

The photographs were prepared by Lieutenant Lawrence Binder.

13. Florman, A. L.: The Use of a Commercially Available Complement-Fixing Antigen for the Diagnosis of Elementary Body Types of Viral Infection, J. Immunol. **51**:29 (July) 1945.

ACNE VULGARIS TREATED WITH VITAMIN A

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AND
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DISCUSSION with dermatologists results in the opinion that the majority have been unable to arrive at a conclusion as to the value of treatment of acne with vitamin A or have judged it to be of little value in spite of the rather favorable report by Straumfjord.[1] Published reports have been few and inconclusive. Experimental studies by Cornbleet and his associates[2] failed to demonstrate any lack of vitamin A in the blood of patients with acne. Obermayer and Frost[3] recently said that as yet they "are prepared only to state that vitamin A therapy is undoubtedly of benefit in the handling of some forms of acne vulgaris while others do not seem influenced by it."

In order to arrive at an opinion, we determined to observe the effects of vitamin A given orally in a dosage of 100,000 units daily to a group of university students with acne. About one third of the group had previously received treatment by other physicians, with little or no effect. Neither they nor those without previous treatment were given any other measure to use while taking vitamin A, and they were given no advice as to diet or hygiene. The duration, extent and severity of their acne varied within wide limits. Patients were asked to return for observation every three to four weeks.

Although 52 patients began the treatment, the reported results are based on observation of 45 patients who continued treatment for an average of four or five months, a period long enough to allow formation of an opinion of the value of the treatment. The majority of the patients were women. In 46 per cent of the cases results could be classed as good, though in only 1 case could the acne be spoken of as cured. Twenty-seven per cent of the patients had slight improvement in their

From the Student Health Service, Dr. Ruth Boynton, Director; and the Division of Dermatology, Dr. H. E. Michelson, Director, University of Minnesota.

1. Straumfjord, J. V.: Vitamin A: Its Effect on Acne, Northwest Med. **42**:219 (Aug.) 1943.

2. Cornbleet, T.; Popper, H., and Steigmann, F.: Blood Vitamin A and Cutaneous Diseases, Arch. Dermat. & Syph. **49**:103 (Feb.) 1944.

3. Obermayer, M. E., and Frost, K.: Some Phases of Vitamin Therapy in Dermatology, Arch. Dermat. & Syph. **51**:309 (May) 1935.

eruptions, and 27 per cent showed no improvement. (Although there was apparent variation based on sexual difference, the series was small and statistical analysis indicated that the difference was probably not significant.)

While no untreated patients were simultaneously observed in order to control the conditions of the experiment, two previously recorded series of comparable material are available for analysis. During a period of observation changes classed as "good" were noted in 55 per cent of a group given nicotinic acid,[4] in 41 per cent treated topically with an estrogenic cream and in 43 per cent using the same cream but without estrogenic content.[5] In comparison with these figures it is apparent that vitamin A does not produce remarkable improvement in acne. In comparison of these results with those reported by Straumfjord, it is noted that he was able to review the results in only 20 per cent of his original group of 300 cases. While 79 per cent were ultimately free or nearly free from the eruption, the improvement usually occurred after three months of treatment and often did not occur until after nine

Results of Treatment with Vitamin A

	Unimproved	Slightly Better	Good	Total
Females	8	8	18	34
Males	4	4	3	11
Total	12 27 per cent	12 27 per cent	21 46 per cent	45

months. In our experience it was usually difficult to persuade the patient to continue oral therapy without other measures when considerable improvement failed to result after six or eight weeks of treatment.

The real value of treatment cannot always be judged by the per cent of persons showing improvement. In this series of patients there were 5 persons who had satisfactory improvement while taking vitamin A but whose eruption became worse after the treatment was stopped, only to improve again when treatment was reinstituted. Are such results the effect of psychotherapy? Such a conclusion seems unjustified since the treatment was offered to these patients without extravagant claims for recognized value. The case of Saunders [6] seems not to be explicable as a result of psychic influence.

4. Lynch, F. W.: Nicotinic Acid in the Treatment of Acne Vulgaris, Arch. Dermat. & Syph. **42**:481-482 (Sept.) 1940.

5. Lynch, F. W.: Treatment of Acne by Local Applications of an Estrogenic Agent, Urol. & Cutan. Rev. **45**:466 (July) 1941.

6. Saunders, T. S.: Favorable Effects of Vitamin A in a Case of Acne of Long Duration, Arch. Dermat. & Syph. **50**:199 (Sept.) 1944.

CONCLUSIONS

The treatment of acne by oral administration of 100,000 units of vitamin A daily seems not to be generally advantageous when continued for only three months. Probably a few persons obtain much improvement with this method of treatment.

LEISHMANIASIS VERRUCOSA OF THE FACE

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BELLO HORIZONTE, BRAZIL

LEISHMANIASIS verrucosa must be studied with special attention because it closely resembles many other verrucous manifestations, such as verrucous syphilides, verrucous tuberculosis and verrucous leproma. The size of the plaque in verrucosa leishmaniasis varies greatly; its outlines are well defined, and it is situated on healthy or slightly erythematous (but never edematous) skin.

The lesion itself is raised and whitish gray and consists in furrows arranged in squares which bound nipple-like projections of uniform height, so that the lesion presents a uniform surface.

According to Canal Feijóo,[1] on inspection one has the impression of looking at a thick crust which completely covers some lesion on which the crust was formed. But when an attempt is made to remove the crust one finds that it is a proliferative lesion. The grooves which divide the nipples are 4 to 5 mm. deep. These nipples are formed of firm tissue, but Canal Feijóo [1] declared that they change their shape under the action of traction or pressure; however, when this traction or pressure ceases, the nipples do not recover their original form. The color of the lesion varies at different levels; it is whitish gray on the surface and pale rose, almost white in its deeper part.

The lesion begins and ends on healthy skin and therefore is not localized on an infiltrated base. It is not exudative but completely dry. Its site of election is the lower limbs. It must be stated, however, that Canal Feijóo [1] (and he alone) saw this lesion in the cervical part of the cephalic region, on the same site where keloidal acne is found. Rabello [2] affirmed that verrucous and frambesical lesions are more commonly met with on the lower limbs. Large verrucous plaques may occur, with, at times, points of regression side by side with spots where the disease is progressing.

My case is worthy of note because of the extremely rare localization of verrucosa leishmaniasis of the face.

---

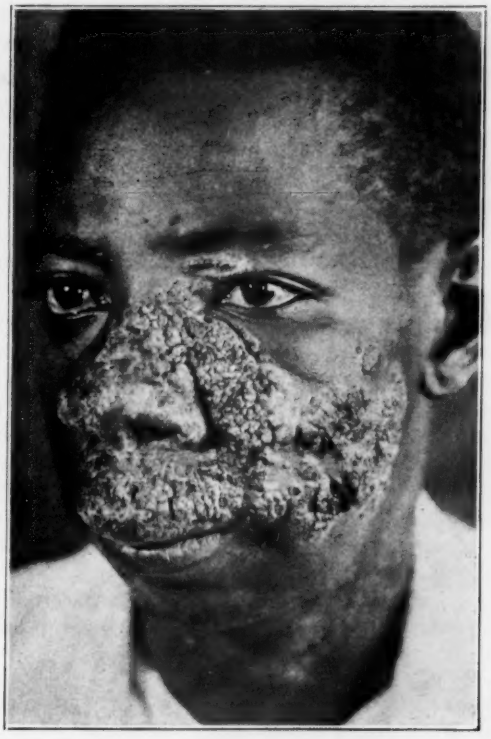
1. Canal Feijóo, E. J.: Particularidades clínicas de la leishmaniosis cutáneo-mucosa observadas en Santiago del Estero, Rev. méd. latino-am. **19**:953-970, 1934.

2. Rabello, E.: Formes cliniques de la leishmaniose tegumentaire, in Deuxième congrés des dermatologistes et syphiligraphes de langue française, Strasbourg, 1923, p. 561.

REPORT OF A CASE

J. P. R. was a Brazilian, a Negro farm worker, residing at Governador Valadares, had a family and personal history of no special interest. General examination showed nothing abnormal. Dermatologic examination showed an extensive lesion covering the back and sides of the nose, the upper lip, the inner part of the left upper eyelid and all the middle part of the left side of the face, as far as the level of the ascending ramus of the lower jaw.

The lesion consisted of a plaque, which was continuous at some points and discontinuous at others. The plaque was all warty, furrowed in various directions and whitish. The edges were well defined and the surface completely dry (fig.).



Leishmaniasis verrucosa of the face.

Laboratory Examination.—Montenegro's test elicited a positive reaction. The Kahn reaction of the blood serum was negative. Histologic examination showed leishmaniasis verrucosa.

SUMMARY

A case of leishmaniasis verrucosa is reported, affecting the face, which is a rare site for this disease.

Rua Ceara, 1691.

CUTANEOUS DIPHTHERIA AND TROPICAL ULCERS

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CAPTAIN MAXWELL H. KOLODNY
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TROPICAL ulcers, of diphtheritic or other origin, have been treated by a variety of methods, with varying degrees of success. With the advent of penicillin, more satisfactory results have been observed.[1] This report concerns itself with the bacteriologic findings and the results of several plans of penicillin therapy in 56 patients with tropical ulcers or ulcerated dermatitides. In 8 of the patients the ulcerated lesions harbored virulent Corynebacterium diphtheriae.

MATERIALS AND METHODS

Plan of Study.—The patients were admitted to special wards with isolation facilities. Schick tests were performed on admission, and the results were read on the third and fifth days, to minimize the number of falsely positive and combined reactions. Each patient was given three days of preliminary cleansing treatments, during which time material for cultures was taken daily from the nose, throat and all active lesions of the skin (ulcerations, fissures, vesicles, pustules and other lesions in which organisms might be found). The preliminary treatment consisted of the application of wet dressings of isotonic solution of sodium chloride from 8 a. m. to 4 p. m. Dressings were kept wet continuously by the application of isotonic solution of sodium chloride; oil silk was not used. To facilitate cleansing and allow access to all portions of the lesions for cultural purposes, the lesions were mechanically débrided of crusts, exudate and membranes with sterile instruments at each change of dressings. No soap, antiseptic or medicament was applied.

On completion of the three day cleansing period, each patient was placed, in rotation and without regard to clinical or bacteriologic findings or results of the Schick test, on one of four plans of treatment.

Plan I (Controls): Compresses of isotonic solution of sodium chloride were applied three times daily for twenty minutes, at 8 a. m., 2 p. m. and 8 p. m. After this, crusts and exudate were removed, pustules or vesicles were opened and the lesions were gently cleansed with sterile isotonic solution of sodium chloride. The surrounding skin was cleansed with 70 per cent alcohol. Dressings made of six thicknesses of fine mesh gauze bandage in 3 inch (10 cm.) lengths were soaked in isotonic solution of sodium chloride. These were firmly applied under gauze fluffs. The dressings were kept continuously wet for two hours.

From the Army Service Forces, Eighth Service Command, Harmon General Hospital, Longview, Texas.

1. Liebow, A. A., and others: Tropical Ulcers and Cutaneous Diphtheria, to be published.

At the end of the two hour period the dressings were removed and the lesions air dried. Dry sterile dressings were applied each night and soaked with isotonic solution of sodium chloride before removal the following morning.

Plan II (Penicillin Locally): Plan II was identical with plan I except that dressings were kept wet for two hours, three times daily, with a solution of sodium penicillin in isotonic solution of sodium chloride containing 250 units per cubic centimeter.

Plan III (Penicillin Parenterally): Plan III was exactly the same as plan I except that, in addition, penicillin was administered intramuscularly in doses of 20,000 units every three hours for seventy-two hours (total dosage 480,000 units).

Plan IV (Penicillin Parenterally and Locally): Plan IV combined plans II and III; that is, penicillin was given locally as in plan II and parenterally as in plan III.

Each lesion under observation was critically evaluated at nine day intervals or earlier if there was obvious deterioration of the lesion. If healing was satisfactory, as manifested by decrease in size or depth of lesion, absence of local surrounding inflammation, lymphangitis, adenitis or development of constitutional symptoms, the treatment was considered a success and continued for another nine day period. If there was a distinct lack of improvement or if the lesion became worse (increased in size or depth, spread to new areas or caused a local reaction or constitutional symptoms) the therapy was adjudged a failure and treatment changed to the plan next in order.

The activity of all patients was restricted. Complete physical and neurologic examinations were made on admission and at frequent intervals during the period of observation. Electrocardiographic tracings were made. Pulse rates were recorded regularly and blood pressures taken twice weekly. Examination of the cerebrospinal fluid was made on most patients.

Patients were discharged from the isolation wards only after all ulcerations were completely healed, three cultures of material from the nose and throat were negative for C. diphtheriae and a final physical and neurologic examination revealed no abnormalities attributable to the local disease. All patients were eventually transferred to the reconditioning section or sent on convalescent furlough, from which they returned for a reevaluation. The effect of activity on the healed ulcerations could thus be evaluated.

Laboratory Procedures.—After the first three days of preliminary cleansing and daily culturing, cultural examinations were made on alternate days throughout the period of observation. For these, Loeffler's serum agar slants, 0.2 per cent potassium tellurite-blood agar and blood agar plates were used. Isolated organisms were obtained in pure culture and identified by their fermentation reactions. The virulence of strains of C. diphtheriae was determined by the lethal test of a guinea pig. In more urgent cases, virulence tests were performed by the intraperitoneal injection of an emulsion of the original cultures suitably diluted. Evaluation of the bacterial flora as a whole was made on the basis of findings on the blood agar plates.

A limited number of direct examinations for other organisms were made of the tropical ulcers. These included dark field examinations for fusospirochetal organisms, sodium hydroxide preparations for fungi, Giemsa-stained scrapings for leishmania and Gram staining for a determination of the general flora. Serologic tests for syphilis were performed routinely; on Negro patients, studies of the blood for sickling of erythrocytes were also made.

RESULTS

Bacteriologic Findings.—Eight virulent and thirty avirulent strains of C. diphtheriae were isolated from 56 patients with cutaneous ulcerations. Organisms were also isolated from the fauces in 1 of the 8 patients with virulent and 14 of the 30 with avirulent organisms. Diphtheroids were isolated in 13 cases (table 1).

Of the 19 cases of tropical ulcers studied, virulent diphtheria bacilli were isolated in 3 and avirulent diphtheria bacilli in 10. Of 15 patients with ulcerations superimposed on an eczematoid dermatitis, C. diphtheriae was found in 12, in only 2 of whom the organisms were virulent. Seven patients had ulcerated lesions superimposed on atypical lichen planus. In 5, diphtheria bacilli were found, in 1 of which the organism was virulent. In a group of 15 patients with ulcerations superimposed

TABLE 1.—*Incidence of C. Diphtheriae in Ulcerations of the Skin and Its Relationship to the Schick Reaction*

	Number of Cases	C. Diphtheriae						Negative for C. Diphtheriae		
		Virulent, Schick			Avirulent, Schick			Schick		
		Number	Negative	Positive	Number	Negative	Positive	Number	Negative	Positive
Tropical ulcer	19	3	3	0	10	6	4	6	5	1
Eczematoid dermatitis	15	2	2	0	10	7	3	3	1	2
Atypical lichen planus	7	1	1	0	4	3	1	2	2	0
Dermatitis, other	15	2	2	0	6	5	1	7	5	2
Totals	56	8	8	0	30	21	9	18	13	5

on any one of several other types of dermatitis, virulent diphtheria bacilli were found in 2 and avirulent bacilli in 6.

All patients with virulent diphtheria bacilli in the cutaneous lesions gave negative reactions to the Schick test. The incidence of positive Schick reactions was comparable in the patients harboring avirulent diphtheria bacilli and in those in whom diphtheria bacilli could not be demonstrated.

From practically every case, hemolytic Staphylococcus aureus was isolated. In somewhat less than 10 per cent of the cases, beta hemolytic streptococci were found. The classification of these organisms was not determined.

Motile and nonmotile forms of Proteus vulgaris were occasionally encountered, but in no case was this organism predominant. Pseudomonas aeruginosa (Bacillus pyocyaneus) was also occasionally isolated; in 1 case it appeared to be the predominant organism.

In none of the cases examined was there found any evidence of fusospirochetosis, localized mycotic infection, leishmaniasis, sickle cell anemia or inadequately treated syphilis.

EVALUATION OF PENICILLIN THERAPY

The Effect on the Bacterial Flora.—Repeated cultural studies revealed that the significant pathogenic organisms (diphtheria bacilli, staphylococci and streptococci) were eliminated in an average period of four days in the patients treated with penicillin locally or penicillin parenterally and locally. In patients treated with dressings of isotonic solution of sodium chloride, either alone or together with parenteral use of penicillin, only some 25 to 30 per cent were cleared of the organisms in an average period of eight days. The value of local use of penicillin and the relative ineffectiveness of parenteral administration of penicillin in these cases are evident (table 2).

In penicillin-treated patients the gram-positive organisms were the first to disappear on culture. In stained preparations, the organisms appeared to have lost their characteristic staining qualities, and a wide

TABLE 2.—*Relationship of Therapy to Bacteriologic Findings* *

Plan of Treatment	Number of Courses	Lesions with Organisms at Start of Course	Lesions Cleared During Course		Lesions Not Cleared During Course	Efficacy, %
			Number	Average Days		
I. Isotonic solution of sodium chloride (control)	20	8	2	8	6	25
II. Penicillin locally	23	11	11	4	0	100
III. Penicillin parenterally	16	10	3	8	7	30
IV. Penicillin locally and parenterally	14	8	7	4	1	90

* These data refer to diphtheria bacilli, either virulent or avirulent. Hemolytic Staph. aureus was found in practically every case and beta hemolytic streptococci in several. These were similarly affected by the various plans of therapy. For several reasons, the role of these organisms could not be studied to an extent comparable with that of the diphtheria bacilli, but their importance in the pathogenesis and healing of the lesions must be recognized.

variation in the size of the organisms was noted. If the local application of penicillin was stopped before healing was complete, it was found that organisms could occasionally again be cultured from the lesion.

The Effect on Healing of Ulcerations (Without Regard to Bacterial Flora).—Practically all patients treated with penicillin locally or locally and parenterally combined showed satisfactory healing of the ulcerations according to the standards previously described. With isotonic solution of sodium chloride alone some healing was observed, but the number of patients showing satisfactory progress was small (35 per cent). A higher percentage (75) per cent showed satisfactory healing following the use of dressings of isotonic solution of sodium chloride together with parenteral administration of penicillin, but the mean healing time was longer. Here again the efficacy of local use of penicillin is clear, for ulcerations which were of two to three months' duration were healed in fifteen to twenty-two days with this care (table 3).

TABLE 3.—*Relationship of Therapy to Healing of Ulcerations Without Regard to Bacteriologic Findings* *

	Age of Lesions and Average, Mo.	Isotonic Solution of Sodium Chloride				Penicillin Locally				Penicillin Parenterally				Penicillin Locally and Parenterally			
			Unsatisfactory Healing	Satisfactory Healing			Unsatisfactory Healing	Satisfactory Healing			Unsatisfactory Healing	Satisfactory Healing			Unsatisfactory Healing	Satisfactory Healing	
		No. of Cases		No. of Cases	Mean Days	No. of Cases		No. of Cases	Mean Days	No. of Cases		No. of Cases	Mean Days	No. of Cases		No. of Cases	Mean Days
Tropical ulcers	1 to 9 (3)	8	7	1	11	8	0	8	18	4	1	3	32	4	0	4	18
Eczematoid dermatitis	1 to 10 (3)	5	2	3	12	6	1	5	12	7	2	5	14	4	0	4	16
Atypical lichen planus	3 to 6 (4)	2	2	0	..	4	1	3	12	2	1	1	25	2	0	2	14
Dermatitis, other	1 to 4 (2)	5	2	3	22	5	0	5	12	3	0	3	22	4	0	4	14
Totals		20	13	7 (35%)	15	23	2	21 (91%)	14	16	4	12 (75%)	22	14	0	14 (100%)	15

* These data do not include effects on the underlying dermatoses.

TABLE 4.—*Relationship of Therapy to Healing of Ulcerations and Clearing of Organisms* *

	Number of Cases Studied	Number of Patients Treated	Number of Patients Not Treated †	Isotonic Solution of Sodium Chloride (Control)			Penicillin Locally			Penicillin Parenterally			Penicillin Locally and Parenterally		
				Number of Courses	Number Successful	Number of Failures	Number of Courses	Number Successful	Number of Failures	Number of Courses	Number Successful	Number of Failures	Number of Courses	Number Successful	Number of Failures
Tropical ulcers	19	16	3	8	1	7	8	8	0	4	3	1	4	4	0
Eczematoid dermatitis (ulcerated)	15	15	0	5	3 ‡	2	6	5	1	7	3	4	4	3	1
Atypical lichen planus (ulcerated)	7	5	2	2	0	2	4	3	1	2	1	1	2	2	0
Dermatitis, other (ulcerated)	15	12	3	5	2 §	3	5	5	0	3	2	1	4	4	0
Totals	56	48	8	20	6 (30%)	14	23	21 (91%)	2	16	9 (56%)	7	14	13 (92%)	1

* Criteria: Successful indicates clearance of the organisms plus satisfactory healing; failure indicates persistence of organisms and/or poor healing.
† Practically healed on admission.
‡ Lesions in 1 case almost healed on admission.
§ One patient had penicillin locally and parenterally shortly before coming to the study ward.

The Effect on Healing of Ulcerations Plus Effect on the Bacterial Flora.—When both the healing process and the bacteriologic findings were considered, it was found that penicillin locally and penicillin locally plus parenterally resulted in the highest percentage of successful courses of treatment (91 and 92 per cent respectively). Dressings of isotonic solution of sodium chloride alone were successful in 30 per cent of the courses; when parenteral administration of penicillin was added, 56 per cent were successful (table 4).

THE HEALING PROCESS

In tropical ulcers treated with penicillin locally, the base assumed a clean, healthy, granular appearance within three to four days. The margins, previously rolled, tended to flatten out. Epithelization occurred from the margins and proceeded rapidly at first but later more slowly as the avascular zone became larger. The central portion was always last to epithelize and usually did so under a scab, which eventually fell off.

In all cases of tropical ulcers, the scar was round or ovoid, flat or depressed, thin and atrophic, with sharply defined borders outlining the original ulcer. It was almost always more deeply pigmented than the surrounding skin. In Negroes the scar was depigmented; keloids were not observed.

In ulcerations superimposed on a dermatitis, healing left little or no scar. The underlying dermatitis, however, was not significantly affected by the penicillin therapy.

COMPLICATIONS

Myocarditis.—No instance of myocarditis was detected either clinically or by electrocardiogram.

Neurologic.—Two cases of peripheral polyneuritis in patients with tropical ulcers were encountered. The cerebrospinal fluid of both patients showed elevated values for the total proteins and no increase in the cellular elements. In another case a suggestive history was obtained, but there was no objective confirmation. Analysis of the cerebrospinal fluid of this person and of all other patients harboring diphtheria bacilli revealed no abnormal values. In both cases of proved peripheral polyneuritis, only avirulent diphtheria bacilli could be isolated. One patient gave a negative reaction to the Schick test. The other gave a positive reaction and so was given 20,000 units of diphtheria antitoxin intramuscularly.

Lymphangitis.—Two cases of lymphangitis were observed. In both the condition arose from infected ulcerations superimposed on eczematoid dermatitis. At the time of onset, 1 patient was being treated with

compresses of isotonic solution of sodium chloride (plan I); the other had completed a course of intramuscular use of penicillin (plan III) eight days previously. Both patients were given penicillin intramuscularly, with rest and elevation of the affected extremities. Improvement was prompt and satisfactory.

Penicillin Sensitivity.—In 4 patients contact dermatitis occurred when penicillin was applied locally; all had previously been treated with penicillin locally in the same cutaneous area. In 4 others preexisting dermatitis became hyperemic, pruritic, edematous and wet within twenty-four hours following the start of parenteral administration of penicillin. In 1 other, a generalized erythematous, maculopapular rash was noted. In 3 patients there developed delayed reactions to parenteral administration of penicillin within seven to ten days following therapy; 2 had urticarial reactions, and in 1 a serum sickness-like syndrome developed.[2]

Recurrences.—There were no recurrences or breakdown of the characteristically thin scar after a thirty day period of normal activity. One patient was admitted while on convalescent furlough from another hospital for a recurrence of a tropical ulcer treated there.

COMMENT

In order properly to evaluate our findings, it should be pointed out that most of the ulcerated lesions were a month or more old and had been treated many times previously with a variety of antibacterial agents. This may in part account for the less frequent finding of virulent diphtheria bacilli, especially in the tropical ulcers, than reported by others.[3] Of 19 cases of tropical ulcer, C. diphtheriae were found in 13, although in only 3 were the organisms virulent. This is comparable to the incidence of virulent diphtheria bacilli found in tropical ulcers occurring in troops in overseas theaters.[4] There is, moreover, reason to suspect that some of the others had at one time harbored virulent organisms, because in 2 of the cases in which only avirulent organisms could be isolated a characteristic peripheral polyneuritis developed.

Virulent diphtheria bacilli were found in almost all varieties of cutaneous lesions and in the nasopharynx as well. It is generally

2. Kolodny, M. H., and Denhoff, E.: Reactions in Penicillin Therapy, J. A. M. A. **130**:1058 (April 20) 1946.

3. Craig, C. M.: A Study of the Aetiology of the "Desert," Septic or Veldt Sore Amongst European Troops and the Association with Faucial Diphtheria, Lancet **2**:478, 1919. Cameron, J. D. S., and Muir, E. G.: Cutaneous Diphtheria in Northern Palestine, ibid. **2**:720, 1942. Medical Circular Letter no. 14, Headquarters United States Army Forces in South Pacific Area, January 1944.

4. Livingood, C. S.: Personal communication to the authors. Liebow and others.[1]

believed that the diphtheria bacillus is unable to penetrate the intact skin, but it is probable that once the epithelial integrity is destroyed, either by trauma or by cutaneous disease, organisms may be introduced and find a suitable medium for growth and toxin production. This is largely supported by the frequency with which trauma precedes the ulcerations from which these organisms were isolated.[1] The onset of the ulcerations in almost half the cases in this series followed trauma. Diphtheria bacilli would thus be fortuitous contaminants, which, once established, might produce pathologic effects in susceptible persons.

The presence of hemolytic staphylococci in almost all the ulcerations indicates some measure of secondary infection, especially in ulcerations preceded by trauma or dermatitis. This is also supported by the finding of a variety of other organisms, all rather frequent contaminants. However, staphylococci may be of greater importance, since their necrotizing power may contribute to ulceration.[5]

Some of the factors involved in the evaluation of the therapy are worthy of emphasis. The plans of treatment decided on were clearly prescribed. Patients were admitted in rotation without selection or regard to clinical or bacteriologic findings. Conditions were maintained constant at all times, with variation in only one factor in the successive plans. Definite standards of evaluation at stated intervals were established and rigidly followed. Two medical officers cared for all patients and consulted each other frequently; there was no change in medical personnel during the course of the study, and, finally, precisely defined nursing procedures were carried out by selected nurses. These factors permitted an objective evaluation of each of the stated plans of therapy.

The data clearly indicate that local penicillin therapy is the treatment of choice in tropical ulcers and cutaneous ulcerations superimposed on one of several types of dermatitis. As would be expected, a few patients healed satisfactorily with rest in bed, good nursing care and compresses of isotonic solution of sodium chloride. A few additional patients responded satisfactorily when penicillin was administered parenterally. Practically all, however, showed progressive healing when penicillin was used locally. Moreover, organisms disappeared more quickly, and the healing time was shortened.

No significant scarring, except in the most extensive lesions, followed the healing of ulcerations which were superimposed on a dermatitis. In the case of tropical ulcers, however, a thin, atrophic and avascular scar remained and outlined the original ulcer. In this series, none has broken down under normal activity. Nevertheless, they can be easily traumatized, and because of the large zone of avascularity healing can be difficult and slow. It is therefore important to treat

5. Unpublished data.

these lesions early, while the ulcer is small, in order to prevent large, avascular scars.

Penicillin alone should not be expected to produce satisfactory healing. Adequate rest in bed, regular cleansing, mechanical débridement, carefully applied dressings and good nursing care were available during the period of this study and are most important adjuvants.

SUMMARY

1. A. The bacteriologic findings in 56 patients with tropical ulcers or ulcerated dermatitides are described. From these, eight virulent and thirty avirulent strains of C. diphtheriae were isolated. Diphtheroids were found in 13 cases.

B. Hemolytic Staph. aureus was isolated from practically all lesions. In slightly less than 10 per cent, hemolytic streptococci were also found. Occasional strains of P. vulgaris and Ps. aeruginosa were encountered.

2. The Schick reaction was negative in all patients from whom virulent diphtheria bacilli were isolated from cutaneous lesions. The incidence of positive Schick reactions in those with avirulent organisms was comparable to that found in patients from whom C. diphtheriae could not be isolated.

3. The cutaneous ulcerations were treated by one or more of four plans of therapy, which included (*a*) dressings of isotonic solution of sodium chloride (control), (*b*) local use of penicillin, (*c*) parenteral use of penicillin and (*d*) penicillin locally and parenterally.

4. An evaluation of the results showed that local use of penicillin yielded the most satisfactory results and is, therefore, the treatment of choice. Evaluation was made on the basis of the bacteriologic findings and the healing of the ulcerations.

5. The methods involved in this evaluation are described and discussed.

6. The importance of rest in bed, mechanical débridement, cleansing, careful dressing and good nursing care is emphasized.

EPIDERMOLYSIS BULLOSA OF THE NEWBORN

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THE CLINICAL history and the observations at necropsy of a 7 week old white girl afflicted with the rare disease epidermolysis bullosa hereditaria are presented. Herlitz [1] in 1935 collected 14 such cases and added 8 of his own. He defined the disease as a familial or hereditary tendency to progressive blistering of the skin and mucous membranes apparent at birth or soon after. Herlitz further stated that this type of epidermolysis differs from the classic simple and dystrophic forms in that it always leads to early death, usually occurring before the third month. Additional cases reported since 1935 are those of Davidson,[2] Brandberg,[3] Schroder and Wells [4] and Black, Wilhelm, Gilbert and White.[5] The case herein recorded is the twenty-seventh.

REPORT OF A CASE

The patient, B. S. H., a 7 week old white girl, was admitted to the University Hospitals on Oct. 29, 1944, with the complaint of recurrent formation of numerous large blisters on the hands, feet and body. According to the mother, the pregnancy was uneventful and the child was born at about term by a normal delivery. Shortly after birth a large vesicle appeared on the upper lip and gum. The mother said that "the skin on the lip and gum seemed to pull away" as the baby's hand was removed from the mouth. The following morning large blisters containing clear fluid were seen on the thumb and about the ankles. Within the next few days vesicles and bullae, some containing clear fluid and others bloody fluid, appeared on the hands, on the wrists, over the knees and about the buttocks and vulva where the diaper rubbed. The lesions were thought by the local physician to be

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1. Herlitz, G.: Congenital, Nonsyphilitic Pemphigus: A Review and Description of a New Disease (Epidermolysis Bullosa Hereditaria Letalis), Acta pædiat. **17**:315-371, 1935.

2. Davidson, L. T.: Hereditary Epidermolysis Bullosa: Report of a Case with a Résumé of the Literature, Am. J. Dis. Child. **59**:371-378 (Feb.) 1940.

3. Brandberg, O. A.: Case of Congenital Pemphigus of Malign Type (Epidermolysis Bullosa Letalis), Ann. pædiat. **157**:162-168, 1941.

4. Schroder, C. H., and Wells, A. H.: Epidermolysis Bullosa in Newborn, Minnesota Med. **28**:128-130, 1945.

5. Black, R. A.; Wilhelm, E.; Gilbert, C. S., and White, C. J.: Epidermolysis Bullosa in the Newborn, J. A. M. A. **129**:734-736 (Nov. 10) 1945.

due to "pemphigus" and were treated with sulfathiazole ointment and a yellow, perfumed, saponifiable oil containing small amounts of hydroxyquinoline, chlorobutanol, hydroquinone and benzoic acid. The mother stated that she had no knowledge of any eruptions of this type in her family or the father's family.

On physical examination the child was well developed and well nourished. The skin was pale with numerous vesicles and bullae, 0.5 to 3 cm. in diameter, on the chest, feet, elbows, heels, vulva and buttocks. The lips were dry and fissured. There were numerous ulcerated lesions of the buccal mucosa bilaterally and on the margins of the tongue. There was one hemorrhagic bulla, 0.5 cm. in diameter, on the middle of the forehead. Most of the bullous lesions contained a clear serous fluid and some a hemorrhagic fluid. The superficial layers of the skin became detached on slight friction (Nikolsky's sign). There were also areas

Fig. 1.—*A*, denuded and ulcerated areas over the skin of the chest and a large bulla over the dorsum of the left hand. *B*, denuded areas of the skin over the buttocks, thighs and right heel, with a large bulla over the external malleolus.

denuded of the superficial layers of the skin and covered by a thin serous film on the left hand and wrist, the right upper lip, the chest and both feet and ankles (fig. 1). They varied from 2 to 7 cm. in diameter. The nails were arched in the center and were laminated. The nail of the third finger of the right hand became detached when cleaned with a pledget of cotton, leaving an oozing bleeding surface. The nails of the third and fourth toes on the right foot were missing. Physical findings otherwise were essentially normal except for a slight enlargement of the cervical lymph nodes. The reflexes were physiologic. The temperature ranged between 99 and 101 F. The Kolmer-Wassermann reaction of the blood was negative on October 27, before the infant's admission to the hospital. The blood contained 8 Gm. of hemoglobin; the red blood cell count was 2,600,000 with decided anisocytosis and some polychromasia; the white blood cell count was 10,000 per cubic millimeter, with 37 per cent neutrophils (nonfila-

mented 21 per cent and filamented 16 per cent) and 48 per cent lymphocytes, 13 per cent monocytes and 2 per cent eosinophils. The child was given multiple vitamins, crude liver extract intramuscularly and vitamin K. Moist packs of isotonic solution of sodium chloride were applied to the denuded areas and a light cradle used for heat over the body. Treatment was of no avail, and the child died at 6:30 a. m. on October 31.

At necropsy (sixteen hours after death) the child was well developed, well proportioned and 50 cm. long and weighed 2,950 Gm. Over extensive areas on the chest, abdomen, back, external genitals, buttocks, thighs, hands and feet there was desquamation of the superficial layers of the epidermis, with crusts over some of the denuded areas. The skin elsewhere remained in folds when pinched or lifted. The scalp was covered with abundant light brown hair and was free of lesions. The anterior fontanel was sunken and measured 4 by 4 cm. The posterior fontanel was closed. The lips were crusted, and the tongue was coated. The hands, fingers, feet and toes were denuded of superficial layers of skin, and some of the nails were missing. The thymus was 2 by 2 cm. and pale pink, with the lobular pattern discernible externally and on its cut surfaces. The lungs weighed 75 Gm. together. The posterior portions were partly airless. Some of the bronchial branches contained aspirated material. The heart measured 3.5 cm. from the base to the apex and 4 cm. across the base. The chambers and their orifices were proportionate and their valves delicate. There were no anomalies of the large vessels or of the coronary sinus and its tributaries. No changes were noted in the peritoneal cavity and spleen, liver, gallbladder and biliary ducts, pancreas, esophagus, stomach and duodenum, jejunum, ileum, colon and rectum. The suprarenal glands, kidneys, urinary bladder, vagina, uterus, fallopian tubes and ovaries were normal.

Microscopic examination was made of the heart, lungs, spleen, liver, pancreas, esophagus, small and large intestines, suprarenal glands, kidneys, urinary bladder, aorta, diaphragm, thymus and skin. In the lungs in focal areas the air spaces contained a few red blood cells, some polymorphonuclear granulocytes and a pink-stained amorphous material. In the septums there were some lymphocytes, plasma cells and large mononuclear cells with occasional giant cells. The cells lining the bronchiolar and bronchial branches were well preserved. In the spleen the malpighian corpuscles were rather large, with decided overgrowth of their germinal centers. Some contained a nuclear debris, free or within large mononuclear cells, and a few polymorphonuclear granulocytes. Scattered throughout the pulp there were minute blood-forming islands. In the liver there were similar blood-forming islands and some slight albuminous and fatty changes. In the tail of the pancreas some of the islands were close to one another, appearing almost confluent. There were no other changes in the acini, ducts or stroma. In the esophagus there was perfect preservation of the surface epithelium, and there were no changes noted in the tunica propria, muscularis mucosae, submucosa and muscular coats. Similarly no pertinent changes were seen in the jejunum, ileum and colon except for aggregations of eosinophilic granulocytes in the tunica propria and changes in the lymph follicles and in the mesenteric lymph nodes similar to those seen in the malpighian corpuscles of the spleen, with numerous eosinophilic granulocytes in the sinuses. In the suprarenal glands the cortical zones were narrow, with some vacuolation of the cytoplasm of the cells. The vacuolation also was seen in the medullary zone. In the kidneys the lumens of the convoluted tubules were almost obliterated by protrusion of vacuolated lining cells. In the urinary bladder the urothelium was well preserved, with the superficial layers in places loose and desquamated. In the thymus the cortical and medullary zones

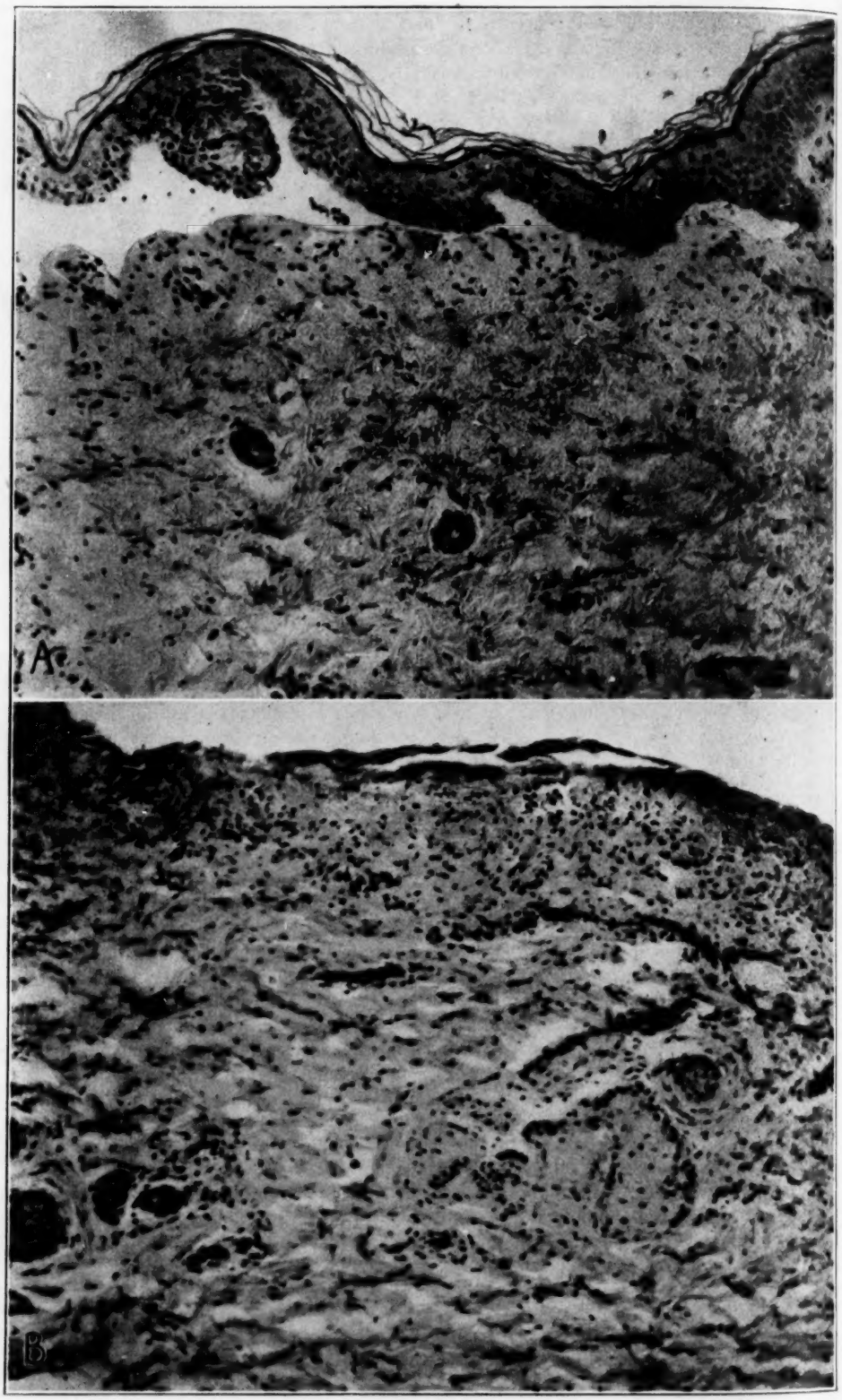

FIGURE 2

(See legend on opposite page)

were proportionate. Hassall's corpuscles were fairly numerous and of good size. Some of them had a concentric debris in their centers. The connective tissue of the septums seemed spread apart. In preparations of the skin stained with hematoxylin and eosin the epidermis appeared to be separated in sheets from the corium (fig. 2*A*). The corium was loose, fibrillar and relatively acellular, with the tissue elements decidedly spread apart. No elastic fibers were seen in preparations stained by Weigert's method. Beneath the superficial layers of the corium there were collagenous bundles, hair follicles, sebaceous glands and sweat glands, the cellular structure of which appeared intact. No change was noted in the subcutaneous adipose tissue. In preparations from the denuded area there was a delicate layer of lavender-stained material with nuclear debris on the surface. In the subjacent portions of the corium there were some infiltrations with polymorphonuclear granulocytes. The deeper layers of the corium, including hair follicles, sebaceous glands, sweat glands and the musculi arrectores pilorum, appeared intact (fig. 2*B*).

COMMENT

An infant in whom extensive bullous lesions of the skin develop at birth or soon after birth presents a diagnostic problem. However, the appearance of the lesions, localization and other circumstances are helpful in establishing a diagnosis. The bullous lesions of syphilis usually appear on the palms and soles, with no apparent relation to trauma. The vesicobullae are always turbid and usually purulent. The oral lesions of congenital syphilis may closely simulate those seen in epidermolysis bullosa, but the serologic reaction of the mother and the presence of concomitant signs and symptoms will aid in verifying them. The presence of similar lesions in other members of the family and other infants in the nursery, as well as the lack of oral lesions, will be of aid in recognizing bullous impetigo. In epidermolysis bullosa hereditaria letalis the lesions result from insignificant trauma (Nikolsky's phenomenon). They occur over the areas exposed to pressure and friction. The bullae usually contain a clear fluid, or they may be hemorrhagic. The nails are loosely attached, and oral lesions are in evidence. History of similar lesions in other members of the family in past generations is of little avail, since Herlitz [1] thought this fatal type of epidermolysis bullosa to be a recessive type. His 8 cases occurred in three families, 4 in one of them and 2 in each of the others. In no instance had there been a previous case in any of the families, all of whom had records to the eighteenth century.

Because the disease at present is not amenable to treatment and is fatal in a short time, early recognition is of the utmost importance.

EXPLANATION OF FIGURE 2

A, microscopic appearance of the margin of a denuded area toward the intact skin, with space between the elevated epidermis and corium. × 152. *B*, microscopic appearance of the denuded area. × 152.

The fundamental nature of this disease is unknown. The defect apparently is in the skin, allowing the epidermis to separate from the corium, and in the mucous membrane of the mouth. It does not involve the entodermal and mesodermal mucous membranes. The mucosae of the esophagus, intestines and urinary bladder in our case were intact. None of the changes observed at necropsy can be regarded as pertinent except those in the skin.

SUMMARY

The clinical history and the observations at necropsy of a 7 week old white girl with epidermolysis bullosa hereditaria are presented. The lesions, consisting in focal separation of the epidermis from the corium and of the epithelium from the tunica propria of the mouth, are present at birth or appear soon after, resulting from insignificant trauma and occurring over areas exposed to pressure and friction. The observations at necropsy suggest that the only structures involved are the skin and mucous membrane of the mouth.

BASAL CELL EPITHELIOMA IN A PSORIATIC PATCH

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BECAUSE of the rarity of epitheliomatous change developing in psoriatic disease, it is felt that a case recently observed is of interest to report.

REPORT OF A CASE

History.—A white man aged 43 was first seen on Sept. 29, 1945. He was admitted to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital for treatment of an eruption that involved the scalp, face, trunk, back and legs, which he first noticed at the age of 12. Since its first appearance he had not been free from it for any length of time. At the age of 21 the eruption practically covered the entire face and the trunk, and he received external palliative treatment. The patient was returned from overseas for psychiatric study. During this survey it was observed that he had psoriasis. A patch on the right side of the body, just beneath the costal cage, was suspected to have undergone malignant change. A histologic examination showed conditions compatible with basal cell epithelioma.

Physical Examination.—The patient did not appear acutely ill and was ambulatory. He had not lost weight and did not appear ill nourished. The pupils were normal and reacted to light and in accommodation. An examination of the anterior segments of both eyeballs revealed no abnormalities. The pharynx and the teeth were normal. There was no cervical lymphadenopathy. Examination of the lungs, heart and abdomen showed nothing abnormal. The blood pressure was 130 mm. systolic and 80 mm. diastolic.

Laboratory Examination.—The urine was normal. The Kahn reaction of the blood was negative. An examination of the blood revealed 100 per cent hemoglobin, 480,000 red cells and 7,200 white cells, with 46 per cent polymorphonuclear leukocytes, 51 per cent lymphocytes, 1 per cent eosinophils and 2 per cent mononuclear cells. The urea nitrogen content of the blood measured 18 mg., the chloride content 450 mg. and the sugar content 87 mg. per hundred cubic centimeters. The basal metabolic rate was + 6 per cent. Porphyrin was not present in the urine.

Dermatologic Examination.—Involving the scalp there were many thick scaly lesions. The areas were ill defined and patchy. On the face, especially the eyebrows, on the nape of the neck and on the back, the lesions were those of typical

psoriasis covered with a micaceous scale, which could be removed. On the chest the patchy eruption chiefly involved the sternal region. These patches varied in diameter from 2 to 5 cm. On the right side of the body, beneath the costal cage, there was a large oblong lesion that clinically appeared as a psoriatic patch (fig. 1). The lesion was well defined, and there was no evidence of ulceration. The border was elevated and was pearly in appearance.

Histologic Examination.—Gross examination showed a specimen that consisted of a tiny fragment of tissue measuring 7 by 2 by 3 cm. The surface presented an irregular scaly appearance and was gray-white and firm. On microscopic examination a portion of the surface was lined by a stratified squamous epi-

Fig. 1.—Psoriatic patches and epitheliomatous plaque.

thelium, which in turn was covered by a layer of lamellated keratin (fig. 2). In several areas there were irregularly shaped masses of basal cells in the corium which were in communication with the basal layer of the epidermis. Many of the cells were spindle shaped, but the outer layer showed definite palisading. The individual cells varied in size, shape and staining characteristics. A moderate number of mitotic figures were encountered. The surrounding tissue of the corium was infiltrated by lymphocytes, plasma cells and monocytes. The appearance of the lesion was not typical of Bowen's disease.

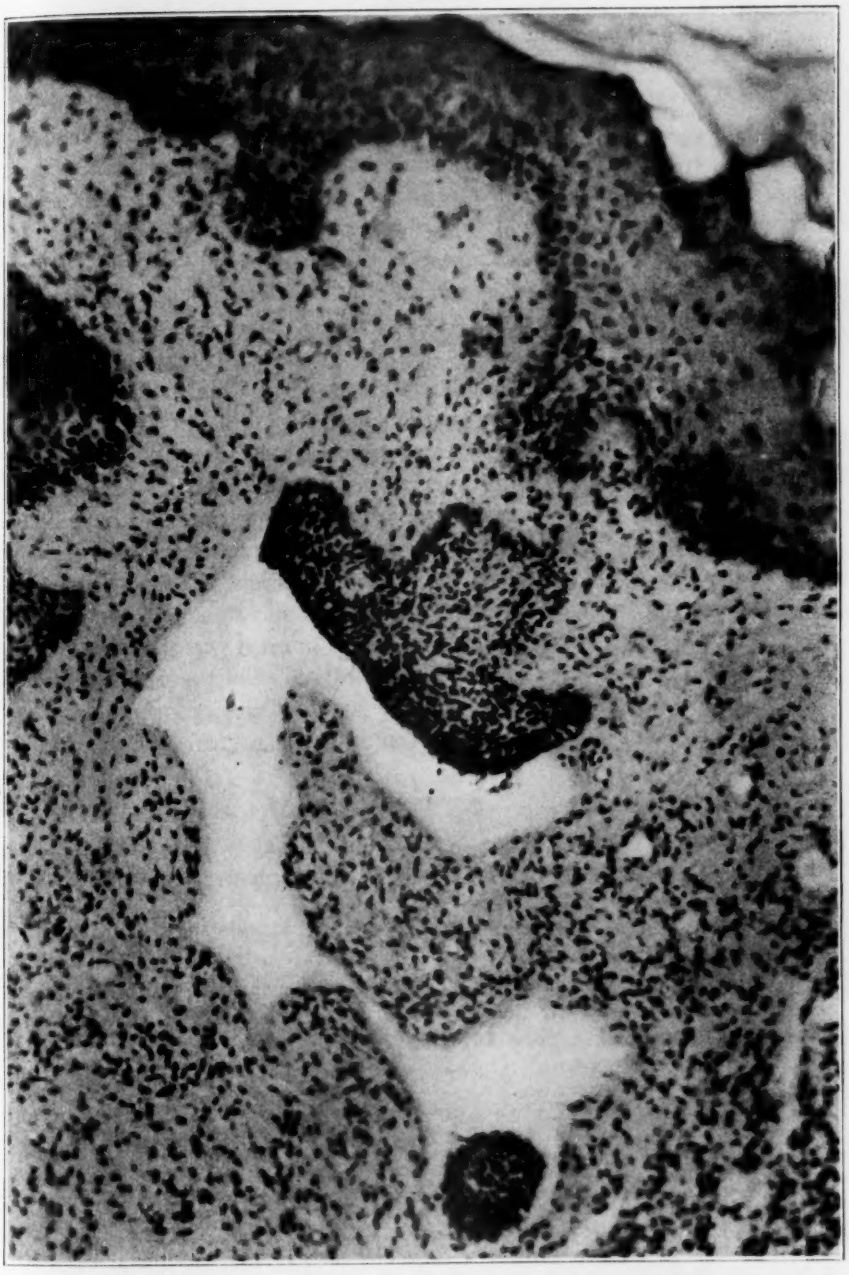

Fig. 2.—Section of skin showing basal cell epithelioma.

COMMENT

The cause of malignant change in psoriasis is unknown. Hartzell [1] in 1899 reported 11 cases. Pozzi in 1874 and Cartaz in 1877 were believed by Hartzell to be the first to report the association of epithelioma and psoriasis. Flint and Gordon [2] recorded a case in which a squamous carcinoma of the scalp was associated with two rodent ulcers on the shoulder which originated in a psoriatic patch. They also mentioned a case reported by Whitfield,[3] in which psoriasis was associated with rodent ulcers, and a case described by Gray,[4] in which a rodent ulcer occurred in a patch of psoriasis in the gluteal cleft. Sequeira [5] stated that he had observed several cases of multiple superficial rodent ulcers that arose in patches of psoriasis. Epitheliomatous changes occurring in 3 cases of psoriasis were completely reviewed in 1933 by Wright and Friedman.[6] In these cases the malignant change did not occur in the diseased skin but rather on normal tissue. All these patients had psoriasis for many years, and in all of them the cutaneous epitheliomas bore a superficial resemblance to the patches of psoriasis. Charache [7] described a case in which the malignant transformation proved to be a squamous cell epithelioma. In our case the patient had had psoriasis for thirty-one years. He did receive local medication, but there was no history of ingestion of arsenic. A point of interest was the recurrence of the psoriatic patch over a period of years and then the final development of a basal cell epithelioma in the area. Other psoriatic lesions were present. The epithelioma was removed by surgical excision.

SUMMARY

A case in which basal cell epithelioma developed on a psoriatic patch is described. The clinical and histologic pictures are presented.

1. Hartzell, M. B.: Epithelioma as a Sequel of Psoriasis and the Probability of Its Arsenical Origin, Am. J. M. Sc. **118**:265, 1899.

2. Flint, E. R., and Gordon, J.: A Case of Squamous Carcinoma of the Scalp, Associated with Two Rodent Ulcers on the Shoulder Originating in a Patch of Psoriasis, Brit. J. Surg. **16**:321, 1928.

3. Whitfield, A.: A Case of Psoriasis Associated with Rodent Ulcer, Brit. J. Dermat. **18**:40, 1906.

4. Gray, A. M. H.: Rodent Ulcer Occurring in a Patch of Psoriasis in the Gluteal Cleft, Brit. J. Dermat. **24**:325, 1912.

5. Sequeira, J. H.: Diseases of the Skin, ed. 4, London, J. & A. Churchill, 1927, p. 558.

6. Wright, C. S., and Friedman, R. J.: Psoriasis and Multiple Superficial Epithelioma, Arch. Dermat. & Syph. **27**:70 (Jan.) 1933.

7. Charache, H.: Squamous Cell Epithelioma in Psoriatic Patches, Arch. Dermat. & Syph. **38**:241 (Aug.) 1938.

TREATMENT OF MYCOTIC INFECTIONS BY INHIBITING RESPIRATION OF DERMATOPHYTES

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IT IS WELL recognized by military dermatologists that mycotic infections in soldiers constitute the most frequent dermatologic complaint. Epstein,[1] in a recent report, stated that "the commonest dermatoses seen in the Army are those due to superficial mycotic infections." This type of cutaneous disease comprised 16.8 per cent of his cases. An analysis of a group of cases by one of us[2] showed that superficial mycotic infections of the feet comprised 11.8 per cent of all cases in which patients reported to the dermatologic clinic. It was also shown that this type of involvement was responsible for more man-days lost than any other cutaneous disease. The realization of the magnitude of the problem has led the Army Air Forces to initiate an extensive study on the prophylaxis and treatment of these troublesome infections. The following report comprises the results of part of that program.

Previous studies in this program on the role of aeration of the feet, accomplished through the wearing of sandals in place of regular issue shoes, in the hygiene of pedal infections have been reported.[3] The present report on a clinical study is an outgrowth of extensive laboratory investigations on the respiration and the inhibition of respiration of the dermatophytes. From those laboratory studies it is believed that the criterion of inhibition of fungous respiration may serve as a useful adjunct to methods at present in use for the selection of fungicidal and fungistatic agents and for elucidation of the mechanism of action of these

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1. Epstein, E.: Dermatologic Practice in a Station Hospital in Southern California: A Comparison with Private Practice, Arch. Dermat. & Syph. **52**:21 (July) 1945.

2. Dolce, F. A.: Mycotic Infections of the Feet Among Soldiers, Mil. Surgeon **97**:152 (Aug.) 1945.

3. Nickerson, W. J.; Irving, L., and Mehmert, H. E.: Effect of Wearing Sandals in Reducing Foot Infections, Air Surgeons Bull. **2**:120-121, 1945; Sandals, and Hygiene and Infections of the Feet, Arch. Dermat. & Syph. **52**:365-368 (Nov.-Dec.) 1945.

agents.[4] In another paper,[5] data have been presented on the rate of oxygen consumption of four species of dermatophytes (microrespirometer determinations) together with the variation in rate for different isolates of a given species; simple methods were developed for handling fungous preparations for the respirometer to insure a minimum of damage to the mycelial organization. The effect of various treatments on the rate of oxygen consumption by different species was determined. The treatments included variation in p_H, variation in salt concentration and addition of selected inorganic compounds and various organic substances in dilute concentrations.

From these experiments some working hypotheses for future investigations were framed in regard to the nature and location within the cell of enzymes controlling respiration and the classes of substances depressing respiration among the dermatophytes. Among the inorganic, water-soluble salts inhibiting respiration, zinc chloride was found to be effective in dilute concentrations.

TABLE 1.—*Effect of Inorganic Zinc Compounds on Oxygen Uptake by Dermatophytes*

Compound	Concentration	Organism	Change from Rate of Oxygen Consumption in Plain Buffer, %
$ZnCl_2$	10^{-2}M	E. floccosum	—92
$ZnCl_2$	10^{-2}M	E. floccosum	—98
$ZnCl_2$	10^{-3}M	T. gypseum	—24
$ZnCl_2$	10^{-4}M	T. gypseum	—13
$ZnCl_2$	10^{-3}M	T. rubrum	—32
Zn acetate	10^{-3}M	T. rubrum	+27
$Zn(NO_3)_2$	10^{-3}M	T. rubrum	—22

It was considered desirable to conduct a clinical trial with zinc chloride to learn whether or not it was of value in the control of superficial fungous infections of the skin. The results of our study are not dramatically in support of zinc chloride, but we feel that the approach of using a compound of known ability to inhibit fungous respiration is of value. Ideally, substances used in treatment of these fungous infections will be toxic to some metabolic process of the fungous mycelium and neutral to the tissues of the host. While respiration is a convenient index of metabolic activity in mycelial organizations of these fungi, there are other indexes that might be investigated; we merely stress that the substance being investigated for toxicity to the fungi be checked for activity against metabolizing mycelial organizations (not solely against spore germination or inhibition of growth).

4. Nickerson, W. J.: Inhibition of Fungus Respiration: A Metabolic Bio-Assay Method, Science **103**:484-486 (April 19) 1946.

5. Nickerson, W. J., and Chadwick, J. B.: On the Respiration of Dermatophytes, Arch. Biochem. **10**:81-99 (May) 1946.

A group of 45 patients with superficial mycotic infections observed in the dermatologic clinic at Eglin Field, Fla., was treated with zinc chloride solution. The cases were classified clinically into three groups: acute, subacute and chronic. There were 24 acute cases, 16 subacute and 5 chronic. The treatment employed in these cases was the local application of a 1 per cent alcoholic solution of zinc chloride (1 Gm. of zinc chloride in 100 cc. of a 25 per cent aqueous solution of alcohol) on the involved areas. This was done once daily in the dermatologic clinic. The treatment was the same in the majority of the cases, regardless of the severity of the infections, organism causing the infection or location. The only departure from this procedure consisted in 10 cases in which an additional application of the solution was used by the patient before retiring and the use of a dusting powder

TABLE 2.—*Clinical and Laboratory Observations in Group of 45 Cases Prior to Therapy*

Diagnosis	Cases, No.	Potassium Hydroxide Examination of Scales	Organism Isolated on Culturing
Tinea capitis	2	Spore mosaic arrangement of ectothrix	M. audouini
Tinea pedis	26	Positive	T. gypseum (20 cases) T. rubrum (4 cases) C. albicans (2 cases)
Tinea cruris	6	Positive	E. floccosum (2 cases) T. gypseum (4 cases)
Tinea pedis et cruris	5	Positive	T. gypseum (4 cases) T. rubrum (1 case)
Tinea glabrosa	6	Positive	T. gypseum (3 cases) T. rubrum (3 cases)

consisting of equal parts of zinc oxide, tannic acid and boric acid. All the cases were grouped together in the final analysis because there was no difference in the therapeutic result. All the patients were treated on a duty status, and no effort was made to curtail their activities. Treatment was continued for an average period of twenty days. In general, treatment was continued until a cure was obtained or there was a steady progression of the infection or an acute flare-up occurred which was considered as a possible result of the treatment. The patients were thoroughly examined prior to treatment. This was done to determine beyond doubt that the cutaneous involvement was mycotic in origin and also to determine the organism responsible for the infection. Table 2 shows the results of that study.

The results of this study indicate that the fungi responsible in these cases were five in number. Two cases of tinea capitis due to infection with Microsporum audouini were included. In the 2 cases the eruptions occurred in children, dependents of Army personnel. Among the soldiers the commonest fungus isolated was Trichophyton gypseum (in 72 per

cent of cases). Trichophyton rubrum was isolated in 19 per cent of the cases. Candida albicans and Epidermophyton floccosum were isolated in 5 per cent of the cases. It was also observed that T. gypseum was isolated in all but 4 of the cases classified as acute. In these 4 cases T. rubrum was isolated in 2 cases, C. albicans in 1 case and E floccosum in 1 case.

The outcome following the use of zinc chloride solution in the group of 45 cases studied was determined. This was done from an analysis of the clinical and laboratory observations. No patient was classified as cured unless all of the following criteria were fulfilled: (1) no clinical evidence of a mycotic infection, (2) potassium hydroxide examinations of scrapings repeatedly negative for fungi and (3) repeated failure to grow fungi from the treated site.

Table 3 summarizes the results of that analysis.

TABLE 3.—*Results of Treatment with 1 per Cent Zinc Chloride Solution Immediately After Treatment*

		Clinical Observation			Potassium Hydroxide Studies		Cultural Studies		
Diagnosis	Cases No.	Cured	Improved	Progression	Positive	Negative	Positive	Negative	Organisms Recovered
Tinea capitis	2	0	0	2	2	0	2	0	M. audouini
Tinea pedis	26	4	17	5	22	4	22	4	T. gypseum (16 cases) T. rubrum (4 cases) C. albicans (2 cases)
Tinea cruris	6	4	1	1	1	5	2	4	T. gypseum (2 cases)
Tinea pedis et cruris	5	0 (pedal) 4 (crural)	3	2	4	1	3	2	T. gypseum (2 cases) T. rubrum (1 case)
Tinea glabrosa	6	3	3	0	3	3	3	3	T. rubrum (2 cases) T. gypseum (1 case)

Eleven patients fulfilled the requirements immediately after the treatment set up for a cure in this study. However, of this group, there were 5 patients in whom the infection recurred after a ten day observation period. The 5 cases were classified as recurrences because the same organism was isolated as on the original investigation and the same site was involved. This reduces the number of cured patients to 6, or 13 per cent. Four cases of recurrence occurred in the group of pedal infections. Thus there were no patients with pedal infections cured. It was evident from a careful analysis and observation of the cases that the use of zinc chloride solution had little or no effect on pedal infections. The improvement noted in the 17 cases of pedal infection was so slight that it would be difficult to ascribe it solely to the use of zinc chloride solution. All the soldiers under treatment were impressed with the proper hygiene of their feet, the necessity of keeping their feet dry and the methods of reducing hyperhidrosis. The improvement noted could well have been due to their improved hygiene of the

feet. Some of the soldiers stated that there was a decided decrease in the itching after the first few applications of the zinc chloride solution. However, their relief was not of a permanent nature, because soon, with continued treatment, all volunteered that the itching returned in the same degree and annoyance as before.

In the group of crural infections there were 4 patients, or 66 per cent, that fulfilled the requirements for cure immediately after treatment. There was 1 patient with a recurrent eruption among these 4 cured patients after an observation period of fifteen days. It was noted that the crural infections responded to this form of treatment more favorably than the pedal infections. This was more forcibly brought out in the group of 5 cases in which both crural and pedal infections occurred. Here the crural infections cleared up or were definitely improved, while the pedal infection was unaffected. There were 6 patients with infections of the smooth skin; 3 were classified as cured and 3 as improved.

It was not possible to draw any definite conclusion from this small group of cases, because of the short period of observation. A comparison with a similar group of patients, treated by the usually advocated methods, showed that the results with zinc chloride solution as employed by us in this study were inferior for pedal infections and approximately equal for crural infections.

The cases were grouped in accordance to the organism isolated and the results obtained. This was done to determine whether there was some difference in response to zinc chloride solution therapy depending on the causative organism.

As a result of the grouping given in table 4, there appeared to be a difference in response depending on the infecting organism. There

TABLE 4.—*Organisms Isolated and Results Obtained*

Organism	Cases, No.	Patients Cured	
		Number	Per Cent
M. audouini	2	0	
T. gypseum	31	3	9.6
T. rubrum	8	1	12.5
E. floccosum	2	2	100
C. albicans	2	0	

was no response to treatment in the infections caused by M. audouini and C. albicans, whereas the 2 patients with eruptions caused by E. floccosum were cured.

A number of complications were observed during the course of zinc chloride therapy:

Lymphangitis	3 cases	29.1 per cent of acute cases
Id eruption on fingers and trunk	2 cases	
Cellulitis	2 cases	

All these complications occurred in the cases classified as acute. Four of the patients required hospitalization after the onset of these complications. It was felt that in some way the use of zinc chloride solution in the acute cases aided the occurrence of these complications. Some of the soldiers complained of smarting, burning and pain following the use of the solution. This was especially so when the solution was applied on a denuded area. In 2 cases not included in this group, the complaints were so great that the zinc chloride was stopped after a few applications. In 3 cases the application of zinc chloride was followed each time by edema and erythema over the involved area. This was transitory and subsided in a few hours.

A number of patients (in addition to those in the group of 45 cases) were treated with a solution of zinc chloride to which had been added 0.25 per cent phenol and 2 per cent salicylic acid. This combination suggested itself following the laboratory investigation in which the addition of phenol and salicylic acid enhanced the in vitro respiratory-inhibitory effect of the zinc chloride on fungi. Although the number of cases in which this combination was tried was too small to draw any conclusions, it seemed a more promising preparation and one which should be given further clinical trial for both pedal and crural infections. This compound was used in cases of tinea glabrosa and in only a few cases of tinea pedis. It was much more effective in the former type of case.

SUMMARY AND CONCLUSIONS

1. A group of 45 patients with superficial mycotic infections observed on an Army post were treated with a 1 per cent alcoholic solution of zinc chloride.

2. Zinc chloride solution, as employed by us in this study, in spite of its action as an inhibitor of fungous respiration in a laboratory investigation, has proved to be inferior to other methods of treatment for pedal infections. Its use in crural dermatoses and in tinea glabrosa seems worth further study.

3. Our purpose in this report has been not to add a new chemical to the already endless list used in the treatment of these troublesome infections but to present a new method of approach, with the hope that this might stimulate further investigation along these lines.

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REACTIONS IN THE TREATMENT OF SYPHILIS WITH PENICILLIN

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GREAT strides have been made in the treatment of early syphilis with penicillin, and reports seem to bear out the belief that penicillin will be an important factor in the management of syphilis. Because of the dominant position assumed by penicillin in the treatment of syphilis, it is important to consider the reactions that may be encountered in the course of therapy. It has been found convenient to classify these reactions in two groups. The first group of reactions is caused directly by penicillin, and the second group of reactions is due indirectly to penicillin and consists in reactions to the products of destruction of the spirochetes.

On review of the literature in the consideration of the first group of reactions, that is, those due directly to penicillin, it is noted that although penicillin has been accepted as the most effective and least toxic chemotherapeutic agent widespread use of this potent antibiotic in various fields of treatment since its introduction has, however, brought forth manifold reports of reaction. According to Keefer,[1] in 2 to 5 per cent of all patients treated with penicillin urticaria developed. The urticaria is usually mild and disappears in spite of the continuance of treatment. In some instances, the urticaria is severe and extensive. Flinn and associates[2] observed cases of severe urticaria from one lot of penicillin. Intradermal tests with this brand and with two others caused positive reactions. Cutaneous tests with a fourth brand elicited negative reactions, however, and administration of this penicillin gave no reaction. Reactions from local application of penicillin were described by Michie and Bailie.[3] The development of bullous dermatitis (dermatitis medicamentosa) was described by Morris and Downing[4] in a patient who had received 1,000,000 units of penicillin for a postoperative infection. In this patient there developed erythema and edema of the

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1. Keefer, C. S.: Am. J. M. Sc. **210**:147 (Aug.) 1945.

2. Flinn, L. B.; McGee, L. C.; Featherstone, W. P., and Kern, D. O.: Delaware M. J. **17**:133 (July) 1945.

3. Michie, W., and Bailie, H. W. C.: Brit. M. J. **1**:554 (April 21) 1945.

4. Morris, G. E., and Downing, J. G.: Bullous Dermatitis (Dermatitis Medicamentosa) from Penicillin, J. A. M. A. **127**:711 (March 24) 1945.

left hand, arm and left side of the body four days after the last injection of penicillin. Tense pitting edema of the entire hand and forearm was present two days after the onset of the reaction. This case showed great similarity to 2 cases which will be described further in the course of this paper. Barker [5] described 2 cases of sensitivity of the skin to penicillin. The first case was that of a medical officer who noted during course of contact with the drug edema of the lids and a vesicular eruption. The second case was that of a soldier in whom, after receiving injections of penicillin for five days, there developed giant urticaria, which persisted for four weeks. Both patients demonstrated positive cutaneous reactions with penicillin.

The Herxheimer reaction has been stated by Stokes to occur synchronously with the hours of greatest destruction of spirochetes by an antisyphilitic drug. This reaction has been postulated to be due either to an irritative reaction to increased liberation of toxins by still living spirochetes or to the protein-decomposition products and endotoxins resulting from their destruction. A review of the literature reveals that this reaction, due indirectly to the action of penicillin and comprising the second group of reactions heretofore mentioned, has been noted by many investigators in the field of penicillin antisyphilitic therapy. Mahoney and colleagues,[6] in one of the first reports on the treatment of early syphilis with penicillin, noted symptoms suggestive of a Herxheimer reaction. More and more reports have come out since then describing this group of symptoms, and they have finally been accepted as a true Herxheimer reaction. Leifer and Martin,[7] in a recent report, stated that 85 per cent of their patients with early syphilis demonstrated a Herxheimer reaction.

In the course of treating approximately 70 patients per month with penicillin for syphilis, the opportunity has been presented to observe numerous and varied reactions. As previously mentioned, these reactions were divided into two groups: (1) those due directly to penicillin and (2) those due indirectly to penicillin (Herxheimer reaction). The first group was further subdivided into three divisions: (*a*) pruritic, (*b*) dermatophytid and (*c*) post-treatment.

REACTIONS DUE DIRECTLY TO PENICILLIN

Pruritic Reactions.—Pruritic symptoms were observed during the first few days of treatment and were similar to those described by Keefer. The patients usually complained of mild generalized pruritus

5. Barker, A. N.: Lancet **1**:17 (Feb. 10) 1945.

6. Mahoney, J. F.; Arnold, R. C., and Harris, A.: Penicillin Treatment of Early Syphilis, Am. J. Pub. Health **33**:1387 (Dec.) 1943.

7. Leifer, W., and Martin, S. P.: Effect of Penicillin on Course of Early Syphilis, J. A. M. A. **130**:202 (Jan. 26) 1946.

and dryness of the skin, and in some a fleeting erythematous eruption was noted. Continued administration of penicillin in this group did not aggravate the symptoms, but instead the symptoms disappeared.

Dermatophytid Reactions.—Reactions directly attributable to penicillin therapy were noted in patients who had fungous infections. In some instances the patients stated that they had been completely free from symptoms of fungous infection at the time the penicillin treatment was begun and that they had suffered symptoms of a dermatophytid reaction after receiving penicillin for a few days.

In the cases in which the infection was already present there was an exacerbation of symptoms. Patients usually complained of a flare-up of the eruption associated with severe pruritus and clinically exhibited the classic picture of a dermatophytid reaction. These findings were explained on the bases of an allergic reaction to a common antigen. The id reaction in these cases is probably due to a common antigen present in the penicillin administered. In a typical case illustrating this type of reaction, the following facts were noted:

On Feb. 17, 1946, three days after commencement of administration of penicillin, the patient (J. R.) noted severe pruritus of the dorsum of the fingers, web spaces and between the toes. He stated that these symptoms were similar to and severer than those experienced during the previous period of fungous infection. The patient gave a history of having had "athlete's foot," which had been absent for some time prior to admission. The lesions exhibited were vesicular in character and present in the areas of pruritus. There was some excoriation between the fingers and toes. The eruption cleared two days after the cessation of penicillin therapy without medication.

Post-Treatment Reaction.—The third group of symptoms directly due to penicillin was noted in patients who had already completed treatment. The following 4 cases illustrate some types of post-treatment reactions to penicillin encountered. It is the experience in this unit that approximately 5 per cent of the patients receiving a full course (one week) of penicillin therapy will show some form of post-treatment reaction, usually a cutaneous one.

J. B. was admitted on the day following conclusion of treatment for primary syphilis. He had received a full week's treatment with penicillin, a total of 1,700,000 units. The patient noted urticaria about twelve hours after conclusion of treatment. On awakening on the day following his departure from the hospital, he noted that his face, forearms, feet and legs were swollen. Associated with this severe swelling he experienced itching over his entire body. He gave no previous allergic history. Physical examination revealed a 45 year old white man who was well built and whose hands, forearms, feet, legs and face were swollen. His eyes were mere slits because of the swelling of his eyelids. There was a pretibial pitting edema (4 plus). The areas swollen were erythematous. There were large urticarial wheals over the thighs and trunk. In the few areas which were moderately clear he exhibited decided dermographia. On the dorsum

of both wrists there were large bullae filled with clear fluid. The conjunctivas were injected.

Clinical Course.—The patient was made comfortable with local applications of calamine lotion wtih 1 per cent phenol and 10 per cent calcium gluconate intravenously. At one point epinephrine was given, without much benefit. The bullae on the wrists broke on the third day of hospitalization, and the edema had completely disappeared by the fourth day. The patient was discharged on the sixth day, with the skin clear except for the denuded areas underlying ruptured bullae. A cutaneous test was made with penicillin and the patient exhibited a pronounced urticarial reaction at the site of the injection.

The patient (P. W.) was admitted complaining of swelling of hands, feet and face, associated with severe pruritus. The patient had received treatment for latent syphilis and was given a total of 3,400,000 units of penicillin over a period of one week. On the fifth post-treatment day he noted gradual swelling of his hands and feet and a severe itching of these regions. The symptoms were slow in onset. The patient gave no previous allergic history. Physical examination revealed a well built, well nourished, light-complected, white, 25 year old man who appeared to be in severe discomfort. The feet were swollen, and pretibial edema (3 plus) was noted. His face and hands were similarly edematous, and most of the regions named exhibited erythema. Giant urticarial wheals were present over the abdomen, back and thighs. The patient complained of severe pruritus, and scratch marks were noted over many portions of his body. As the patient stated, he looked like "a swollen boiled lobster." His temperature was 100 F.

Clinical Course.—During the first and second days the temperature was elevated to as high as 102 F. He was given rest in bed, bland diet and calamine lotion with 1 per cent phenol to control the pruritus. He also received calcium gluconate intravenously and barbiturates orally. He showed improvement and was discharged after four days of hospitalization. The edema subsided on the third day of hospitalization.

A patient (W. S.) was treated for latent syphilis over a period of one week and noted the onset of urticarial wheals over the lower part of the abdomen and back twelve hours after the completion of penicillin treatment. There was severe pruritus associated with the wheals. The condition resolved itself one day after onset. A cutaneous test on the forearm with penicillin in this case produced large urticarial wheals on the forearm.

A patient (V. S.) received 3,400,000 units of penicillin over a one week period of treatment and noted a macular eruption over his arms, back and neck twenty-four hours after the therapy was completed. The reaction disappeared after being present for one day. There was a moderate amount of itching associated with this eruption. The cutaneous test with penicillin in this case also elicited a positive reaction.

REACTION DUE INDIRECTLY TO PENICILLIN (HERXHEIMER REACTION)

The second group in this classification—and in our mind the most important group of reactions noted—was classified as a Herxheimer reaction. The Herxheimer reaction was observed in approximately 90 per cent of the patients with early syphilis treated. The characteristics of the Herxheimer reaction noted in the order of their frequency were fever, chills, edema and pain at the site of the lesion, nausea, general malaise, headache and pains in the joints. Although the Herx-

heimer reaction is not a penicillin reaction per se, since it is felt by many to be a reaction to the products of destruction of the spirochetes, it has been emphasized in this paper because it is a fairly constant finding in patients with early syphilis treated with penicillin.[8] In a typical case, the patient usually notices fever from two to eight hours after the beginning of treatment. The fever is soon followed by chills and pain at the site of the primary lesion. These symptoms and the other symptoms noted previously usually persist from twelve to twenty-four hours after the beginning of treatment. In cases of secondary syphilis, arthralgia and general malaise are more commonly encountered than in primary syphilis. A fairly constant finding in secondary syphilis is the flare-up of eruptions after penicillin therapy has been begun. Frequently in cases of primary syphilis in which careful examination of the skin previously revealed no eruption present eruptions of secondary syphilis appeared after the commencement of penicillin therapy, sometimes to fade within four to twelve hours.

COMMENT

The reactions encountered in the course of treatment of syphilis with penicillin can be classified into two groups. In the first group are included the reactions due directly to penicillin. In this classification are included the symptoms which appear shortly after treatment has been begun and pass away in spite of the continuance of penicillin administration. This reaction group may be termed the "early treatment pruritic reaction group." Only approximately 5 per cent of the patients treated exhibited this form of reaction. The "dermatophytid reaction group" provides the second category of reactions noted. It is suggested that the active principle responsible for this reaction is an antigen present in penicillin. This reaction has been noted in the administration of various brands of penicillin. It is my impression that a common antigen exists in both the penicillin and the fungus responsible for the past or present infections. The most serious types of reactions were encountered in the "post-treatment reaction group." The symptoms were varied as to type, time of onset, severity and duration. In some, the severity of the reaction necessitated hospitalization. In the more serious conditions, serum sickness accompanied severe reactions of the skin. This group is similar to reactions noted in other papers and probably is due to sensitization developed over a long period of administration of penicillin.

The Herxheimer reaction in early syphilis treated with penicillin comprises the second group of reactions noted, or reactions due indi-

8. Fromer, S.; Cutler, J., and Levitan, S.: Masking of Early Syphilis by Penicillin Therapy in Gonorrhea, J. Ven. Dis. Inform. **27**:7 (July) 1946.

rectly to penicillin. The findings, namely, fever chills, edema and pain at the site of the chancre are fairly typical. This reaction, because of its frequency in early syphilis treated with penicillin, should be added to the other findings, viz., history of exposure, symptoms presented, clinical picture and positive results on dark field examination, which are usually recorded in a well rounded picture of a case. Its addition provides further significant evidence in the complete, final diagnosis of early syphilis.

In no case in which reactions directly attributable to penicillin were noted could any one brand of penicillin be incriminated, because in the course of treating any one patient many brands were used.

SUMMARY

1. Review of the literature reveals that more and more types of reactions to penicillin are being noted during and after penicillin therapy.

2. Observations in the treatment of syphilis with penicillin revealed that there were four types of reactions encountered. These reactions were divided into two groups and three subdivisions: I, reactions due directly to penicillin ([*a*] early treatment pruritic [*b*] dermatophytid and [*c*] post-treatment) and II, reactions due indirectly to penicillin ([*a*] Herxheimer reaction).

Dr. John C. Cutler tendered many helpful suggestions in the preparation of this paper:

UNDECYLENIC AND PROPIONIC ACIDS IN THE PREVENTION AND TREATMENT OF DERMATOPHYTOSIS

CAPTAIN MARION B. SULZBERGER (MC), U.S.N.R.
AND
COMMANDER ABRAM KANOF (MC), U.S.N.R.

THIS article summarizes the results of three large series of experiments performed under the direction of the Research Division of the Bureau of Medicine and Surgery of the United States Navy. The object of the experiments was to ascertain as accurately as possible the efficacy of certain fatty acids and their salts in the prophylaxis and treatment of dermatophytosis.[1]

The first and third studies were made at the United States Naval Disciplinary Barracks, Hart's Island, New York, during the later part of the summer of 1944 and throughout the summer of 1945.[2] In these two experiments a comparatively small number of men were studied under the particularly favorable experimental conditions, arising from the fact that the subjects were all prisoners and could be kept under close and constant observation and control. These men were studied by the Hart's Island paired comparison method. This method consists in the application of two different agents simultaneously to bilateral, symmetrically situated areas of skin and the evaluation of their relative efficacy. As used here, one remedy was applied to one foot and a second to the other foot of the same volunteer. The technic and advantages of the procedure have already been described.[3]

The second series of studies was carried out in three different Naval establishments, all situated in Florida, in locations where semitropical

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The opinions or assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

1. In this report the terms "dermatophytosis" and "fungous infection" should not be taken literally. They are employed here to designate the signs and symptoms commonly attributed to fungous infection of the feet.

2. Shaw, H. C.: Comparative Evaluation of Preparations for the Prophylaxis and Treatment of Fungous Infections of the Feet and Groins by Means of Screening Tests in Human Volunteers, Report of Research Project X-448, Bureau of Medicine and Surgery, 1945. Sulzberger, M. B., and Kanof, A.: Comparative Evaluation of Preparations for the Prophylaxis and Treatment of Fungous Infections of the Feet, Report of Research Project X-448, Report No. 2, Bureau of Medicine and Surgery, 1945.

3. Sulzberger, M. B.; Shaw, H. C., and Kanof, A.: Evaluation of Measures for Use Against Common Fungous Infections of Skin, U. S. Nav. M. Bull. **45:** 237-248 (Aug.) 1945.

climatic conditions were approximated.[4] In these studies different groups of men used one agent on both feet. The incidence of infection for each medicament was recorded for each different group instead of comparing the efficacy of two agents by applying one to each foot of the same person.

The details of the conditions under which the experiments were carried out, of the experimental procedures and of the results obtained are given in references.[5]

The formulas of the fatty acid preparations studied were as follows:

	Per Cent
Undecylenic acid–undecylenate powder[6] (pigmented)	
Zinc undecylenate[6]	20.0
Purified talc, U. S. P.	76.0
Undecylenic acid, grade AA	2.0
Dibenzo thio indigo (red)	2.0
Sodium propionate powder[6] (pigmented)	
Sodium propionate (Mycoban)	20.0
Purified talc, U. S. P.	79.5
Polychloro copper phthalocyanine (green)	0.5
Sopronol powder[7] (pigmented)	
Calcium propionate	15.0
Zinc propionate	5.0
Purified talc, U. S. P.	79.5
Polychloro copper phthalocyanine (green)	0.5
Undecylenic acid–undecylenate ointment[6] (pigmented)	
Undecylenic acid, grade AA	5.0
Triethanolamine	3.0
Zinc undecylenate[6]	18.0
propylene glycol, N. F.	10.0
Carbowax 1500	19.0
Carbowax 4000	29.6
Distilled water	15.0
Dibenzo thio indigo (red)	0.4

In addition, the following powders were included in these studies:

	Per Cent
Boric acid–salicylic acid powder[8] (pigmented)	
Salicylic acid, U. S. P. (powder)	2.0
Boric acid, U. S. P. (impalpable powder)	6.0
Zinc stearate, U. S. P.	3.0
Purified talc, U. S. P.	86.5
Dibenzo thio indigo (red)	2.0
Polychloro phthalocyanine (green)	0.5
Diodoquin (powder)[8]	
Diodoquin	5.0
Purified talc, U. S. P.	95.0
Vioform (powder)[9]	
(*a*) Vioform (powder) 1.0 (*b*) Vioform (powder)	3.0
Purified talc, U. S. P. 99.0 Purified talc, U. S. P.	97.0
Talcum powder	
Purified talc, U. S. P.	100.0
Foot powder, U. S. N., contract #N140S-14632A	
Sodium bicarbonate, U. S. P.	10.0
Sodium borate, U. S. P.	5.0
Kaolin, N. F.	35.0
Purified talc, U. S. P.	38.0
Sodium perborate, U. S. P.	10.0
Titanium dioxide	1.0
Chlorthymol, N. F.	0.5
Methyl salicylate, U. S. P.	0.5
Thiourea (powder)	
Thiourea	5.0
Purified talc, U. S. P.	95.0

4. Shaw, H. C.: Comparative Evaluation of Preparations for the Prophylaxis and Treatment of Fungous Infectious of the Feet and Groins: II. Report of Studies Made Under Field Conditions in a Subtropical Climate, Report of Research Project X-448A, Bureau of Medicine and Surgery, 1945.

5. Footnotes 2, 3 and 4.

6. Supplied by Wallace & Tiernan Products, Inc., Belleville, N. J.

7. Supplied by Mycoloid Laboratories, Inc., Little Falls, N. J.

8. Supplied by G. D. Searle & Co., Chicago.

9. Supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

INCIDENCE OF DERMATOPHYTOSIS

For the purpose of recording the natural incidence of infection, only experiments II and III are summarized here. Experiment I is omitted because it included only a few men. In experiments II and III relatively large numbers of men were studied, and the two experiments were conducted during approximately the same period. Results were as follows:

A. Unselected Men (men in whom infections were found at the beginning of the experiment, in the course of routine examinations conducted to select subjects for the prophylactic studies).—

	Men Examined	Incidence of Infection, %
Florida (March to August 1945).....	4,720	23.8
New York (May to July 1945).....	1,152	14.0
Total	5,872	21.9

B. Selected Men (men having uninfected feet at the first examination and used as "controls").—These figures show the incidence of foot infection while under observation and without treatment or prophylactic measures.

	Feet Examined	Incidence of Infection, %
Florida (March to August 1945).....	2,768	28.0
New York (May to July 1945).....	531	30.9

(In the men from Florida both feet were untreated during the experiment. In the men from New York, one foot was powdered daily with one of the agents and the other foot was the untreated control included here.)

The statistics confirm the fact that dermatophytosis is a widespread disease. The greater initial incidence in Florida over that in New York was to be expected. It was rather unexpected to find that in both experiments there developed in the men under observation a greater incidence of infection than that found in the random group at the beginning. It had been thought that the greater consciousness of foot hygiene on the part of the men assigned to the experiment might lower the rate of infection. On the other hand, the men in the experiment were observed repeatedly for infection throughout the warmest season, while those in the random group were examined only once and chiefly in the spring.

PROPHYLAXIS OF DERMATOPHYTOSIS

The results of the use of the various agents are summarized in the three tables.

TREATMENT OF DERMATOPHYTOSIS

At Hart's Island during the summer of 1945, 70 men in whom the two feet showed an equal degree of infection were treated with the undecylenic acid–undecylenate ointment on one foot and the unde-

cylenic acid–undecylenate powder on the other. In 15 men the feet treated with the ointment healed on the average one week quicker than those treated with a powder. In 9 men the feet treated with the pow-

TABLE 1.—*Experiment I, at Hart's Island, New York (Summer 1944)*

Foot	Preparation Used	Feet, No.	Infections	
			No.	%
Right	Undecylenic acid–undecylenate powder	137	1	0.7
Left	Boric acid–salicylic acid powder	137	15	10.9
Right	Undecylenic acid–undecylenate powder	144	2	1.4
Left	Sodium propionate powder	144	7	4.9
Right	Boric acid–salicylic acid powder	114	13	11.4
Left	Sodium propionate powder	114	4	3.5

TABLE 2.—*Experiment III, at Hart's Island, New York (Summer 1945)*

Group	Series	Foot		Feet, No.	Infections, No.	Infection, %
I	A	Right	Undecylenic acid–undecylenate powder	107	6	5.6
		Left	No treatment	107	51	47.7
	B	Right	Undecylenic acid–undecylenate powder	106	4	3.8
		Left	Calcium propionate powder	106	8	7.5
	C	Right	Undecylenic acid–undecylenate powder	108	7	6.5
		Left	Talcum powder	108	25	23.1
	D	Right	Undecylenic acid–undecylenate powder	107	4	3.7
		Left	5% thiourea powder	107	21	19.6
	E	Right	Undecylenic acid–undecylenate powder	111	12	10.8
		Left	Foot powder, U. S. N.	111	26	23.4
II	F	Left	1% and 3% vioform powder	118	5	4.2
		Right	No treatment	118	18	15.3
	G	Right	Foot powder, U. S. N.	119	13	10.9
		Left	No treatment	119	34	28.6
	H	Right	Calcium propionate powder	105	16	15.2
		Left	No treatment	105	49	46.7
	J	Right	5% diodoquin powder	82	2	2.4
		Left	No treatment	82	12	14.6

TABLE 3.—*Experiment II, in Florida (Summer 1945)*

Agent Used (Both Feet)	Men, No.	Incidence of Infections		Reduction of Incidence of Infection, %
		No.	%	
No prophylactic agent	1,384	387	28.0	Control
Undecylenic acid–undecylenate powder	1,213	48	4.0	85.7
Calcium-zinc propionate powder	814	64	7.9	71.8
Boric acid–salicylic acid powder	648	98	15.1	46.1
Sodium propionate powder	135	20	14.8	47.1

der healed on the average one and one-third weeks earlier than those treated with the ointment. In 44 men healing time was the same with both powder and ointment. In 2 men the experiment could not be continued to completion.

In general, the therapeutic results confirmed the finding of the prophylactic series in placing undecylenic acid–undecylenate preparations first among the agents studied. The following figures are abstracted from experiments at Hart's Island and in Florida.

Agent Used	Men, No.	Cured or Improved, %	Unchanged or Worse, %
Undecylenic acid–undecylenate powder..	489	81	19
Sodium propionate powder.....	164	75	25
Boric acid–salicylic acid powder.....	221	48	52

SUMMARY AND CONCLUSIONS

1. Intensive investigations by the Hart's Island method of paired comparisons, followed by extensive clinical trial on a large group of men in subtropical areas, were employed to ascertain the relative efficacy of various agents in the prevention and treatment of fungous infections of the feet.

2. In one large clinical study, the prophylactic use of undecylenic acid–undecylenate powder was found to reduce the incidence of dermatophytosis by 85 per cent.

3. The following nine agents were compared as to relative prophylactic efficacy. They are listed in approximately descending order of the efficacy found:

1. Undecylenic acid–undecylenate powder
2. Diodoquin, 5 per cent talcum powder
3. Vioform, 1 to 3 per cent in talcum powder
4. Calcium–zinc propionate powder
5. Sodium propionate powder
6. Foot powder, U.S.N.
7. Boric acid–salicylic acid powder
8. Talcum powder
9. Thiourea, 5 per cent in talcum powder

4. Therapeutically, undecylenic acid–undecylenate powder was slightly more effective than sodium propionate powder, which in turn was definitely more effective than the boric acid–salicylic acid powder.

5. Therapeutically, there was no significant difference between the efficacy of undecylenic acid–undecylenate powder and undecylenic acid–undecylenate ointment.

6. Approximately one quarter of all the men studied and examined had clinical evidence of active fungous infection of the feet.

Clinical Notes

USE OF THE PURPLE X BULB IN DIAGNOSIS OF FUNGOUS DISEASES OF THE SCALP

CHARLES C. DENNIE, M.D., and DAVID B. MORGAN, M.D.
KANSAS CITY, MO.

A suitable substitute has been found for the ordinary glass Wood filter. The latter is advantageous in the diagnosis of fungous infections, especially those of the scalp. The substitute is a 250 watt light bulb with nickel and cobalt incorporated in the glass wall of the tube, which thus supplies radiation near the longer wavelength ultraviolet bands. It is made by the General Electric Company. This bulb was designed for the testing of minerals, paints and certain inks that have fluorescing properties. It is known as number 250 A-21-60 natural red purple, Purple X bulb. It sells for $1.25, and, although the filaments are fragile and may be broken easily in shipment, each intact bulb will last for at least fifty hours of intermittent use. It also has the advantage of fitting any medium light socket designed for 115 volts and operates on either alternating or direct current. However, since the filament operates at a high temperature, the lamp should be used only in a porcelain socket and should never be placed in contact with combustible materials. For protection of the patient and operator, a reflector should cover one half of the bulb and a wire mesh screen can be placed over the open side of the lamp and attached to the reflector. Thus, all that one needs is a small, floor type lamp stand which can be bent in any desired direction and a small dark room.

Microsporon infections of the scalp stand out vividly as a greenish phosphorescence on illumination with this bulb, almost identical in color with that seen with a true Wood filter. The extent of tinea versicolor may also be readily established. To date we have not had any experience with endothrix or leptothrix infections.

Because of the ease of manipulation of this bulb and its low cost, we feel that it will be found most convenient for all dermatologists to have at their disposal, either in their own offices or in clinics. Many physicians do not employ either the Wood filter glass or the filtered ultraviolet lamps that are now on the market. The former is cumbersome because it must be attached to an ultraviolet light by a black canvas focusing cloth, while the latter are expensive compared with the light we have described. Commercial lamps used for indoor photography also provide a source of ultraviolet irradiation, but for this use again a Wood filter attachment is necessary.

These Purple X bulbs can be economically placed in schools for diagnosing or ruling out ringworm of the scalp and can be operated by the school nurses. Private patients with tinea capitis, living at a great distance, can buy one of the bulbs for use in their homes, particularly when there are several children in the family. It is easy to teach the parents the use of this light, in order that they may follow the patient's progress.

A standard 100 watt ultraviolet projector lamp has been compared with this bulb, and the latter has been found just as efficient in producing fluorescence in the several instances of tinea capitis in which both types of lamps were used. In the examination of treated patients, final determination of cure has been the same with both lamps. We cannot be too emphatic in stressing the value of filtered

ultraviolet irradiation as a most necessary criterion for final determination of cure of tinea capitis. It is also felt that three examinations, with normal results, at weekly intervals are necessary to be certain that cure is complete.

Dr. Ralph Mueller, of Kansas City, Mo., an orthopedic surgeon, suggested the use of this lamp, as he has used it in crystallography, his avocation.

1524 Professional Building.

POSSIBLE BENEFIT FROM PROTEIN HYDROLYSATES FOR EXFOLIATIVE DERMATITIS

NORMAN R. GOLDSMITH, M.D., LANCASTER, PA.

This observation is submitted in the hope that it may initiate study and verification by physicians who have access to more clinical material than I.

I am reporting 2 cases of chronic generalized exfoliative dermatitis in which the patients appeared to improve from oral therapy with amino acids after usual measures had failed.

REPORT OF CASES

CASE 1.—The skin of a white man aged 64 had desquamated for two and a half years. According to him, the attack had started from industrial "oil poisoning" and had resisted all previous attempts at treatment. After fourteen days of ingestion of protein hydrolysate, four months previous to the writing of this paper, he was almost well.

CASE 2.—In a white woman aged 28, with a definite history of psoriasis for at least ten years, there developed generalized exfoliation of five months' duration. Six weeks after receiving amino acids orally, she showed large islands of normal skin.

Both patients had had the usual supportive therapy, including intramuscular injections of liver extract and soothing topical applications, but neither seemed to improve until the oral administration of the protein hydrolysates.

It is hoped that others will investigate the possibilities of this new, simple, practical aid for what is so often an extremely difficult therapeutic problem.

Abstracts from Current Literature

EDITED BY DR. HERBERT RATTNER

PALMAR ERYTHEMA—ITS RELATIONSHIP TO PROTEIN DEFICIENCY. RICHARD M. JOHNSON and HANS H. HECHT, Am. J. M. Sc. **211**:79 (Jan.) 1946.

Palmar erythema has been described as a familial disorder associated with pregnancy, cirrhosis of the liver, pulmonary tuberculosis, rheumatoid arthritis and a wide variety of other diseases. Its frequency is indicated by the authors' observation of 93 instances of palmar erythema in examination of 1,183 patients. It occurred in all ages of both sexes and in a wide variety of diseases. Hypoalbuminemia occurred in 83 per cent of the patients with palmar erythema and in 62.5 per cent of an unselected group of patients in the same hospital, and this difference was regarded as significant.

Johnson and Hecht do not regard hypoalbuminemia as the cause of palmar erythema, but the findings of palmar erythema in a patient should suggest the probable existence of a protein deficiency.

CHLOROMA—A CLINICO-PATHOLOGIC STUDY OF 2 CASES. E. G. GOODMAN and LALLA IVERSON, Am. J. M. Sc. **211**:205 (Feb.) 1946.

Chloroma represents a rare form of myeloblastic leukemia in which the cells show an unusual tendency toward tumor formation. Its rarity is indicated by the fact that the 2 instances reported in this paper are the only ones in which the conditions were so diagnosed at Duke Hospital among 226,796 patients. In both instances tumors were the presenting signs, and the clinical course was rapidly downhill. In 1 case, in a 7 year old Negro boy, twelve small, firm, pea-sized, movable nodules developed.

LYNCH, St. Paul.

ONCHOCERCIASIS. J. G. SCOTT, Am. J. Ophth. **28**:624 (June) 1945.

Scott found the following ocular complicatons in 342 Cameroon soldiers, all of whom were assumed to be infected with Onchocerca: punctate keratitis, 61 cases; punctate keratitis with iridocyclitis, 27 cases, and presence of microfilarias in the aqueous of otherwise unaffected eyes, 16 cases. Retrobulbar neuritis, atrophy of the optic nerve and choroiditis occurred rarely. The microfilarias of Onchocerca volvulus were the commonest (if not the only) microfilarias to enter the anterior chamber. Their presence was well tolerated. The cause of complications was a toxin (probably filarial and possibly microfilarial). The common occurrence of nonencapsulated filarias (O. volvulus) is postulated.

W. ZENTMAYER. [ARCH. OPHTH.]

ACUTE PORPHYRIA: CLINICAL AND PATHOLOGIC OBSERVATIONS. MAX BERG, Arch. Int. Med. **76**:335 (Nov.-Dec.) 1945.

In an unusual case of acute porphyria, Berg made observations on the status of the capillaries of the skin during the acute attack, noting extreme spasm of the capillaries and evidence of injury to some of the capillaries in the form of aneurysmal dilatation. In addition, definite alterations in gastric contractility were recorded. He states that the bullae arising in the skin as a result of exposure either to sunlight or to direct trauma may be related to the increased permeability of the capillaries, which in turn is the result of the injury to the capillary.

VENOSPASM: ITS PART IN PRODUCING THE CLINICAL PICTURE OF RAYNAUD'S DISEASE. MEYER NAIDE and ANN SAYEN, Arch. Int. Med. **77**:16 (Jan.) 1946.

Naide and Sayen point out that physicians do not have a clear concept of what is meant by the term Raynaud's disease, and they discuss some of the outstanding opinions. In 10 patients with Raynaud's disease they thought that the clinical features in only 1 were those produced by arterial spasm alone; in 8 both venospasm and arterial spasm were required to produce the picture, and in 1 venospasm alone was present. In the 4 patients with Raynaud's phenomenon, the symptoms were part of a generalized scleroderma, and in 2 of these patients there was evidence of both venous and arterial spasm. The authors use the term "Raynaud's disease" to describe an exaggerated vascular response to cold and to emotional tension with bilateral, symmetric digital involvement. The term "Raynaud's phenomenon" is reserved for digital vasospasm, secondary to other known pathologic conditions such as scleroderma, arthritis and cervical rib.

The observations of the authors lead to the conclusion that in this group of vasospastic disorders the clinical picture varies depending on the intensity of constriction in arteries and in veins and on the type of vessel in which abnormal constriction predominates. It is emphasized that spasm of the veins as well as of the arteries is present in the majority of these patients. Arterial spasm alone cannot explain the clinical picture in most patients. Naide and Sayen also point out that Raynaud's disease is not rare; the milder forms are fairly common and do not deserve the connotation of seriousness usually associated with the diagnosis, and reassurance is an important part of treatment.

RELATIONSHIP OF BOECK'S SARCOID AND TUBERCULOSIS: REPORT OF A CASE IN WHICH TUBERCULOSIS OF LYMPH NODES WAS ASSOCIATED WITH FEATURES HIGHLY SUGGESTIVE OF SARCOID. JUSTIN R. DORGELOH and PAUL W. TULLY, Arch. Path. **40**:309 (Nov.-Dec.) 1945.

A 9 year old child had painless cervical adenopathy with redness of the adherent overlying skin. There was no cutaneous reaction to old tuberculin or purified protein derivative. The patient also had hyperglobulinemia. Excision was performed, and the sections showed both tuberculoid structure and fairly characteristic sarcoid reaction. Because of the pathologic changes, hyperglobulinemia and anergy to tuberculin, the authors state that this case lends additional weight to the argument that sarcoidosis, in some instances at least, is an atypical reaction to tubercle bacilli or their products.

SCLEREMA ADIPOSUM NEONATORUM OF BOTH INTERNAL AND EXTERNAL ADIPOSE TISSUE. PEARL ZEEK and ETHEL MAE MADDEN, Arch. Path. **41**:166 (Feb.) 1946.

There is a generally accepted opinion that subcutaneous fat necrosis of the newborn and nonsuppurative panniculitis are confined to the external adipose tissues. For this reason Zeek and Madden describe a case with widespread involvement of adipose tissue, both internal and external, with lesions which were histologically typical of subcutaneous fat necrosis of the newborn. No other such case was found recorded in the available literature. Because previous studies have apparently been incomplete, it cannot be stated whether this case represents an exception to a general rule or whether the internal lesions have been missed heretofore.

LYNCH, St. Paul.

STUDIES ON POISON IVY AND OTHER DERMATITIS-PRODUCING PLANT PARTS WHEREIN ACTIVE, RESINOUS PRINCIPLES ARE SUSPENDED IN AQUEOUS SOLUTION. MARGARET B. STRAUSS and W. C. SPAIN, J. Allergy **17**:1 (Jan.) 1946.

Reported observations seem to indicate that more than one toxic substance is present in the ivy plant capable of causing dermatitis venenata in susceptible persons. The same is true of poison oak, poison sumac, primrose and other plants.

The poison ivy extracts available at the present time for testing or treatment by the parenteral route are either alcoholic or oily solutions of an oleoresin of the ivy plant. Each of these extracts has objectionable features.

By a special method, which they describe in detail, the authors prepared an "extract" in an aqueous medium. They found the new product nontoxic and nonirritating and as active as an equivalent dilution of the alcoholic ivy extract. Sensitive patients who were treated prophylactically with this preparation "were relieved by the second to fifth injection." Twelve patients who were treated prophylactically in 1943 with an alcoholic extract, with poor results, were treated with this extract in 1944, "with good clinical results." Sixteen other persons treated in a similar manner in 1945 showed "excellent clinical results."

Guinea pigs were sensitized by one intraperitoneal injection of this preparation, as shown by positive reactions to patch tests with 3 drops of a concentrated solution of this extract or alcoholic ivy extract twenty-one days after the sensitizing injection.

AN ALLERGIC REACTION FOLLOWING TYPHUS-FEVER VACCINE AND YELLOW-FEVER VACCINE DUE TO EGG YOLK SENSITIVITY. SIMON S. RUBIN, J. Allergy **17**:21 (Jan.) 1946.

The author reports a case of angioneurotic edema in a 19 year old soldier, involving the eyelids, bridge of the nose and both cheeks. The eruption appeared one and one-half hours after he had received inoculations of typhus fever and yellow fever vaccines, and it was associated with blocking of the nose and pain in the chest.

Scratch tests elicited negative reactions to chicken feathers, chicken meat and egg white and a positive (4 plus) reaction to egg yolk. Intradermal tests with freshly prepared extracts gave doubtful reactions to egg white in dilutions of 1 : 1,000 and 1 : 10 and a positive (4 plus) reaction to egg yolk in a 1 : 1,000 dilution. Passive transfer tests elicited a negative reaction to egg white, a positive (3 plus) reaction to egg yolk, a positive (1 plus) reaction to yellow fever vaccine in a 1 : 100 dilution and a positive (2 plus) reaction to typhus vaccine in a 1 : 100 dilution.

The patient had not eaten whole eggs since infancy because they caused him to vomit; he could eat the white of hard-boiled egg without any trouble. For the past eight years he had had early and late hay fever.

The author concludes that the allergic manifestations were due to sensitivity to egg yolk and calls attention to the allergic potentialities of these vaccines.

ANAPHYLACTIC SHOCK FROM SKIN TESTING: TWO CASES—ONE FATAL. OSCAR SWINEFORD JR., J. Allergy **17**:24 (Jan.) 1946.

The author reports 2 cases of anaphylactic shock from intracutaneous tests with food extracts. One case terminated fatally. The food which caused the fatal reaction was not determined; the nonfatal reaction was thought to be due to mustard.

In each case, anaphylactic shock occurred before the cutaneous reaction was fully developed.

CONTACT DERMATITIS DUE TO ACE ADHERENT. ANDREW G. FRANKS, J. Allergy **17**:112 (March) 1946.

The author observed 4 cases of contact dermatitis due to "Ace Adherent," a preparation employed to obtain skin traction in amputees. The dermatitis (scaly, erythematovesicular) was confined to the area where the adherent was applied. In 1 case, a generalized urticarial eruption followed the appearance of the local reaction.

A patch test with the "Ace Adherent" elicited a "severe reaction necessitating the removal of the test material after four hours."

The ingredients of Ace Adherent include Galex (a dehydrogenated rosin), Venice turpentine, tannic acid, gum camphor and ethyl alcohol. The author suspects Galex as the cause of the dermatitis.

MENDELSOHN, New York.

HOSPITAL MORBIDITY AND MORTALITY OF INFANTILE ECZEMA. STEPHAN EPSTEIN, J. Pediat. **26**:541 (June) 1945.

The occurrence of severe complications and even of death among infants hospitalized because of infantile eczema has led to repeated warnings that children with eczema should not be admitted to a hospital but should be taken care of at home or at a foster home. The author presents a report on 100 consecutive infants with eczema admitted to a hospital from 1937 to 1944. In this series no deaths occurred. Of these 100 children, 21 suffered from twenty-three complications, and there was a morbidity of 21 per cent. A breakdown of these statistics shows that all but one of the complications occurred among the 78 children with atopic eczema and one among the 22 with nonatopic eczema. Nearly all complications were infections of the respiratory tract or gastrointestinal disturbances. They are explained by the author as exacerbations of concomitant respiratory or gastrointestinal allergy. These statistics demonstrate that with the advent of sulfonamide compounds and with proper nursing care there need not be fear of death in hospitalized infants with eczema.

This conclusion should not lead to indiscriminate hospitalization of patients with infantile eczema, but it should eliminate fear in the instances in which the severity of the eczema or other circumstances make hospitalization mandatory.

The so-called sudden death from eczema is discussed. A hypothesis of toxic effects from phenol-like tar products, in combination with interference with cutaneous respiration and disturbance of the autonomous nervous system, is suggested to explain this phenomenon. A reminder is given about the toxicity of coal tar, and it is suggested that tar preparations should not be used over too great surfaces.

AUTHOR'S ABSTRACT. [AM. J. DIS. CHILD.]

PITYRIASIS RUBRA PILARIS AND VITAMIN A. ARTHUR D. PORTER and E. W. GODDING, Brit. J. Dermat. **57**:197 (Nov.-Dec.) 1945.

A case is reported of pityriasis rubra pilaris in which there was improvement following therapy with vitamin A. In attributing improvement to vitamin A, the authors realize that it is unwise to draw conclusions from a single case, especially in a disease which is apt to undergo spontaneous remissions.

While it cannot be maintained that pityriasis rubra pilaris is purely a deficiency disease, yet the clinical and histologic appearance of the skin, the therapeutic effect of large doses of vitamin A and the dark-adaptation tests do indicate that vitamin A is implicated at some stage.

The various factors that might be concerned include intake, absorption, conversion of carotene to vitamin A, storage, circulation levels, synthesis of vitamin-protein compounds required by different tissues (e. g., photochemical pigments) and the ability of the tissues themselves to utilize these compounds.

The cause of the disease in regard to vitamin A remains at the moment largely speculative. Whatever the cause, it appears that liability to the disease is inherited.

THE FUTURE OF B. P. OINTMENTS. A. R. G. CHAMINGS, Brit. J. Dermat. **58**:1 (Jan.-Feb.) 1946.

The author considers four main types of skin which should be considered with respect to any particular form of medication: (1) the average greasy skin, with a normal moisture content; (2) the dry though greasy skin; (3) the moist skin, characterized by excessive sweating, and (4) the exceedingly dry skin, defective in both moisture and grease content and readily susceptible to pathologic conditions.

The four general states of the skin enumerated should not be treated with the same base. When the principle is accepted that in general a water-containing medium should be applied to the skin, it would seem that for three of the conditions specified an oil in water emulsion would be desirable, while for the others—the excessively moist skin (no. 3)—the water in oil type would be indicated. The latter is at present represented by hydrous ointment prepared from ointment of wool alcohols B. P., on which work is presumably still being carried out in order to produce a more satisfactory preparation. For the oil in water base, one prepared with Lanette wax SX would appear to be preeminently satisfactory.

A greasy base should still be included in the pharmacopeia, and white ointment is as good as any, though its emulsifying tendency would perhaps be obviated by the use of hydrous instead of anhydrous wool fat.

BLUEFARB, Chicago.

REPORT OF FORTY-EIGHT CASES OF MARGINAL BLEPHARITIS TREATED WITH PENICILLIN. M. E. FLOREY, A. M. MCFARLAN and I. MANN, Brit. J. Ophth. **29**:333 (July) 1945.

Forty-eight patients with blepharitis were treated with local application of penicillin ointment containing 600 to 800 units of penicillin per gram of base. Staphylococcus aureus was isolated from the lesions of 39 of 41 patients examined bacteriologically. Thirty-six of the patients applied their ointment regularly three or four times a day for as long as it was considered necessary (i. e., three to ten weeks). Recovery took place in all these patients without removal of other foci of infection or any adjuvant treatment other than epilation of a few lashes. Bacteriologic observations were found to be closely associated with clinical signs, but the disappearance of Staph. aureus from cultures of material from the lids was considered a better indication for cessation of treatment than clinical signs, as it invariably succeeded clinical improvement. A follow-up study a year after treatment was discontinued revealed that two thirds of the patients reporting had remained free of recurrence without further treatment.

W. ZENTMAYER. [ARCH. OPHTH.]

STUDIES IN DENERVATION. J. DOUPE and Associates, J. Neurol. & Psychiat. **6**:94 (July-Oct.) 1943.

Methods.—Doupe and his co-workers carried out a number of investigations on patients with lesions of the peripheral nerves. The methods used consisted in measurement of the peripheral circulation by means of recording cutaneous temperatures of the finger pads, supplemented in some instances by plethysmographic records of the digits. Various measures to modify the circulation, such as local effects of moderate to extreme cold or heat and injections of epinephrine, were used.

The Circulation in Denervated Digits.—Investigations were carried out to test the validity of the hypothesis of Lewis and Pickering that sympathectomized limbs stay warm while denervated digits become cold. Observations were made on subjects with preganglionic and ganglionic sympathectomies and on subjects with lesions of peripheral nerves. Doupe concluded that contrary to the results of Lewis and Pickering, the digital vascular reactions are similar in the two groups of patients. The cause of the usually diminished circulation in denervated digits is sensitization to cold produced by degeneration of the sympathetic fibers. This sensitization is made the more manifest by the action of circulating epinephrine by the action of vasomotor fibers still supplying the limb and by variations in local and general blood pressure. Part of the difference in the state of denervated and ganglionectomized digits may be ascribed to the persistence in the latter of some postganglionic fibers. The reactive hyperemia which has been observed in denervated digits is in part mediated by arteriovenous anastomoses, is not dependent on any neural mechanism, is greatly slowed by a high sympathetic vasoconstrictor tone and is not affected by the vasoconstriction caused by cooling the denervated digit. Denervated blood vessels appear to be histologically normal.

There is no correlation between Raynaud's syndrome and sensitivity associated with denervation. In the former condition there is no hypersensitivity to epinephrine. In the latter there is no history suggestive of vasospasms, the cyanosis is slight and there is a ready response to reactive hyperemia. Thus, with lesions of peripheral nerves the blood flow is adequate to the needs of the tissue, while with Raynaud's syndrome ischemia occurs. The trophic changes in denervated digits are attributed to the lowered tissue metabolism consequent on the persistent coldness, since the blood supply is adequate. The sensitivity to cold in denervated digits may be explained on the basis of changes in hydrogen ion concentration, since a fall of temperature would directly raise the p_H and produce vasoconstriction or decrease the formation of acid metabolites and thus indirectly lead to elevation of the p_H and vasoconstriction. The regain of tone following denervation is ascribed to the action of local influences on sensitized vessels. A circulating vasoconstrictor substance in the blood may only be assumed in the case of systemic disorders.

Inflammation and Trophic Ulcers in Denervated Areas.—Slow healing of trophic ulcers produced by burns or pressure in denervated digits has been ascribed to diminished blood supply. Since the authors contend, however, that the blood supply of denervated digits is adequate, there must be other causes for the delayed healing. In the case of ulcers following burn, the slow healing is only apparent, since data are lacking on the extent of the original trauma because of loss of pain sensation in the denervated area. In the case of ulcers produced by pressure, slow healing is due to edema associated with impairment of the lymph drainage in the extremity. The occasional presence of a vesicular eruption in cases of peripheral nerve lesions also is due not to denervation but to a variety of cheiropompholyx.

Mechanism of Axonal Vasodilation.—On the basis of a case of section of the ulnar nerve, Doupe concludes that axonal vasodilation is mediated by fibers other than those associated with sensation. The mechanism of axonal vasodilation is still obscure. According to Lewis, it depends on efferent cholinergic fibers having their trophic center in the posterior root ganglions and distributed in the skin in the form of a plexus, stimulation of which releases the so-called H substance. A review of the literature fails to corroborate this view. The author offers an alternate hypothesis, viz., that the fibers subserving axonal vasodilation are afferent and that they terminate in a branching axon system with receptors specially sensitive to products of tissue damage, similar to histamine. Axonal vasodilation is thus attributed to the metabolites of nerve fibers rather than of cells of the skin.

Epinephrine.—Denervation of digital vessels in human subjects renders them hypersensitive to the vasoconstricting action of epinephrine. This is due to degeneration of sympathetic fibers, which produces in the vessels of denervated digits a lowered threshold and a prolonged response to the action of epinephrine. The vessels of preganglionectomized digits, on the other hand, show only a lowered threshold. This difference between degenerative and nondegenerative section of sympathetic nerves is due to a loss of "accommodation" in the former which is not present in the latter. Emotional stimuli cause a release of epinephrine in the body, but the need for heat conservation is a more variable and less constant cause of such liberation. Thus, the original view of Cannon that secretion of epinephrine is associated with mental excitement is more correct than his later assumption that epinephrine participates in many of the ceaseless variations in body function. Peripheral neurogenic vasoconstriction is not necessarily accompanied with the release of epinephrine, an indication that within the sympathetico-adrenal system different patterns of behavior are elicited by stimuli of different types. Epinephrine could be liberated in the body in amounts comparable to the rapid intravenous injection of 2 micrograms or to injection of the drug for longer periods at the rate of 6 micrograms per minute. In other circumstances, much larger amounts might be liberated, which would suffice to initiate persistent vasoconstriction in a denervated digit.

Circulation in the Skin of the Proximal Parts of the Limbs.—Doupe and his collaborators confirmed the view expressed by Grant and Holling that there exists a vasodilator sympathetic supply to the blood vessels in the skin of the proximal parts of the limbs by producing active vasodilation in response to intense heating of the body. The lack of effect of nerve block when the subjects are cold shows that there is no significant vasoconstrictor innervation of the vessels in these areas of the skin. The vasodilation is not dependent on the activity of the sweat glands, since the action of the latter can be abolished by atropine without thereby decreasing the vasodilation. The thesis of Grant and Holling is not refuted by the occurrence of vasodilation following sympathectomy. The latter phenomenon may be due to discharges in vasodilator fibers, which are decentralized by the operation, to the anesthetic and to absorption from traumatized tissues.

Sebaceous Secretion.—The author and his co-workers estimated the sebaceous secretion in a subject with a sympathectomy and in another subject with a lesion of the brachial plexus. They found that the sebaceous glands can function in the absence of all nerve fibers. Similarly, the growth of hairs and the metaplasia of the cells of the epidermis are unaffected by deprivation of direct nerve influences. Sebaceous secretion is thus simply a manifestation of the growth of the cells of the sebaceous glands. The physical state of the skin influences the production and absorption of the sebaceous material. The abundant secretion in cases of lethargic encephalitis may be due to disturbances in hormonal regulation.

Effect of Electrical Stimulation on the Circulation and Recovery of Denervated Muscle.—The value of electrical treatment of denervated muscles was investigated in a series of 12 patients after suture of the musculospiral or the posterior interosseous nerves. It was found that electrical treatment had no beneficial effects on the return of motor power. This failure was ascribed to the fact that the treatment does not impose a strain on the muscles of sufficient intensity to be of therapeutic value. The amount of electrically induced exercise was estimated by using the rate of blood flow as an index, and it was found that even more intensive stimulation produced a relatively slight increase in blood flow. The only benefit derived from electrical therapy is in induction and reeducation of muscular movements.

Contractility and Excitability of Denervated Muscle.—The electrical reactions of denervated muscles consist in changes in contractility and excitability. Repetitive excitation is likely to develop in denervated muscle when it is subjected to an electric current. This phenomenon is a persistence of potentials throughout the phase of muscle shortening, due to the fact that each muscle fiber is responding more than once. It is readily produced by a constant current. The phenomenon of galvanotonus is also attributed to the repetitive firing of the muscle fibers. Denervated muscles usually show prolonged contraction, which is due to repetitive stimulation by constant currents in conjunction with a cool state of the muscle. Similarly, denervated muscles show prolonged excitation, which is also due to repetitive stimulation plus the relation of the muscle fibers to the field of the current. Electrical reactions are of clinical value only when positive, for when negative they may be attributed to factors other than the state of degeneration of the muscles.

MALAMUD, San Francisco. [ARCH. NEUROL. & PSYCHIAT.]

FAVUS. C. H. WHITTLE, Proc. Roy. Soc. Med. **38**:229 (March) 1945.

A case of favus in a boy of 6½ years is reported. The condition was diagnosed as psoriasis when the child was first seen, because of the absence of fluorescence under the Wood light, but on examination some of the hairs and scales were found to contain abundant fungous elements, chiefly coarse branching hyphae.

WILLIAMSON, New Orleans. [AM. J. DIS. CHILD.]

Society Transactions

NEW ENGLAND DERMATOLOGICAL SOCIETY

Bernard Appel, M.D., *President*

G. Marshall Crawford, M.D., *Secretary*

April 11, 1945

Xanthoma Disseminatum (also Tuberosum et Planum). Presented by Dr. John G. Downing, Boston.

F. C., a 44 year old white man of Irish-American descent, was presented from the Massachusetts Memorial Hospitals. Five years ago the patient noted the appearance of yellowish lesions on the palms and a yellowish tint in his eyes. The lesions gradually became generalized. Some loss of weight and fatigue were also apparent. Three years ago an examination revealed an enlarged liver. For the past year the yellowing of the skin has been progressive. The urine has been dark, and from five to six light brown stools have been passed daily. He has been increasingly fatigued.

At this time the patient presents deep jaundice of the skin, mucous membranes and scleras. Numerous nevi aranei are seen on the upper part of the trunk and the neck. The palms, flexor creases of the fingers, cubital fossae, axillary folds, neck, face and eyelids reveal multitudes of small, flat, pale yellow papules. In the axillary areas these have coalesced. Pinhead-sized papules are diffusely scattered over the remainder of the surface of the skin, with coalescence at pressure areas. These are most profuse on the extensor surfaces of the forearms. On both elbows there are nodular lesions, approximately 1 cm. in diameter. The liver is tremendously enlarged (the edge was palpable 10 to 12 cm. below the right costal margin in the midclavicular line), firm and nodular. The spleen is also moderately enlarged.

Laboratory findings were as follows: serum bilirubin content, 19.32 mg. per hundred cubic centimeters; icteric index, 75, and alkaline phosphatase level, 56 King-Armstrong units (normal 7 to 14). The urine contained bile (4 plus). The total cholesterol content amounted to 447 mg., and the cholesterol esters to 250 mg. per hundred cubic centimeters.

DISCUSSION

Dr. Walter F. Lever: I think that it is of interest that the cutaneous lesions preceded the jaundice in this patient. As far as I know from the literature, in most cases jaundice precedes cutaneous lesions, often by many years. It has been a much discussed question whether hepatic disease can cause xanthomatosis or whether the xanthomatosis is primary and the hepatic disease secondary. A case like this would favor Thannhauser's contention that the xanthomatous disease is primary and the biliary cirrhosis secondary, due to xanthomatous deposits in the bile ducts.

Dr. Bernard Appel: The diagnosis is primary essential xanthomatosis of hypercholesteremic type with secondary biliary cirrhosis. That is the type that Thannhauser classifies as xanthoma planum et tuberosum.

Dr. John G. Downing: Eusterman and Montgomery (Eusterman, G. B., and Montgomery, H.: Disorders of Liver and Extrahepatic Biliary Ducts Associated with Cutaneous Xanthomas and Hyperlipemia, *Gastroenterology* **3**:275 [Oct.] 1944) reported a fatal case of the condition occurring in a woman 48 years of age seen at Mayo Clinic. She showed all the physical signs of the patient exhibited today. She also had severe hyperlipemia. They stated the belief that this is consistent with Thannhauser and Magendantz' concept of essential xanthomatosis

as seen in so-called xanthomatous biliary cirrhosis. The authors stressed that cutaneous xanthomatosis and hyperlipemia occasionally occur in association with primary disease of the liver (so-called xanthomatous biliary cirrhosis) and in association with hepatic disease that is secondary to obstruction of the common bile duct, especially as the result of postoperative stricture. In cases in which the hepatic disease is primary the prognosis is generally unfavorable. It is more favorable in cases in which the underlying pathologic process is due to obstruction of the common duct.

Xanthoma Disseminatum. Presented by Dr. John G. Downing, Boston.

M. F. B., a 48 year old white woman, is presented from the Massachusetts Memorial Hospitals.

Her illness began three years ago with generalized pruritus, progressive yellowing of the skin, loss of weight and frequent epistaxis. Two years ago she noted discrete yellow lesions on her eyelids and forearms, following which the eruption became more widespread. Within the past year there has been no discernible change in the jaundice or cutaneous manifestations, but the patient has had three severe hemorrhages from the gastrointestinal tract. The site of bleeding has not been determined.

A deep jaundice is evident throughout the patient's skin, mucous membranes and scleras. The palms, cubital spaces, axillas, neck and eyelids reveal multiple plaques of assorted sizes which are composed of coalesced, slightly raised, flat-topped, pale yellow papules. On the anterior aspects of the thighs, discrete yellowish papules of a follicular type are found. The liver is greatly enlarged, firm and nodular. The spleen is not palpable.

The laboratory findings were as follows: serum bilirubin content 16.3 mg. per hundred cubic centimeters and alkaline phosphatase content 45 King-Armstrong units. The total cholesterol level amounted to 500 mg. per hundred cubic centimeters. The urine contained bile (4 plus).

DISCUSSION

Dr. George E. Morris: I should like to suggest that this patient is suffering from xanthoma eruptivum and xanthoma diabeticorum. She has lesions which are red and pruritic on her legs, which is not xanthomatosis of the tuberosa type.

Dr. Walter F. Lever: Patients with primary xanthomatosis of the hypercholesteremic type may have secondary xanthomatosis, or the eruptive form of xanthomatosis, which is due to lipemia. It is often referred to as xanthoma diabeticorum, but this is not a correct designation, because not hyperglycemia but the hyperlipemia frequently associated with diabetes causes the lesions. Frequent epistaxis and gastrointestinal bleeding may be due to a deficiency in vitamin K. I remember a case of primary xanthomatosis that came to autopsy two months ago. The patient had originally come into the hospital because of uncontrollable epistaxis. The only way of stopping the bleeding was by giving large doses of a preparation of vitamin K intramuscularly and orally, which helped as long as it was given.

Dr. Malcolm Stanley (by invitation): If I may review briefly his classification, Thannhauser divided the disease into primary, or essential, xanthomatosis and secondary xanthomatosis. The secondary type is associated with hyperlipemia, oftenest due to uncontrolled diabetes, occasionally von Gierke's (glycogen storage) disease and rarely familial hyperlipemia. The last is characterized by different types of xanthoma, particularly the kind which was called xanthoma eruptivum, which both these patients have, or have had, and which is believed to be due to the hyperlipemia with biliary obstruction. The serum in these cases is of differential diagnostic significance, milky in the secondary varieties and clear in the essential types.

The primary, or essential, types are divided into three classes: the hypercholesteremic, the normal cholesteremic and a combination of the two. The hyper-

cholesteremic type is characterized, according to Thannhauser, by xanthoma planum et tuberosum, tendon xanthoma, xanthoma of the coronary arteries and the vascular system in general, xanthoma of the biliary system and xanthoma palpebrarum. The normal cholesteremic type is characterized by xanthoma disseminatum, with occasional osseous and pulmonary involvement; there are no tuberous xanthomas and no involvement of the tendon sheaths, coronary arteries or biliary tract. I believe that the distribution of these (disseminate) lesions is particularly on the flexor surfaces, as today's patients have shown, in the axillas and on the neck. Then there is the third type, the combination of the two.

The 2 patients who are shown here have xanthomatosis of the essential hypercholesteremic type, with blood cholesterol values in the neighborhood of 500 mg. per hundred cubic centimeters (normal 150 to 200 mg.) and a clear serum. Both patients, however, show cutaneous lesions of all types (planum et tuberosum and disseminate and eruptive varieties of xanthoma), both primary and secondary, and both have biliary cirrhosis. In the second patient the jaundice came on before the xanthomas were seen by her. She had three severe gastrointestinal hemorrhages. In both cases the prothrombin time has always been within normal limits. It is well known that these patients have epistaxis. Gastrointestinal hemorrhages are better explained by xanthomas in the tract itself. In dogs, if the common bile duct is tied, ulcers will appear in the duodenum at the level of the ampulla of Vater. This does not apply in the present instances, since there is obviously plenty of bile getting into the duodenum, as determined by the normally pigmented stools. Another possible explanation is esophageal varices, though they were not demonstrable in the second patient. She has had three massive gastrointestinal hemorrhages, and one cannot find out why; all one can do is to give her transfusions.

To speak for a moment about the biliary cirrhosis, the woman has definitely xanthomatous biliary cirrhosis, proved by operation, biopsy and cholangiogram. It is known, therefore, that the jaundice is not due to extrahepatic obstruction. The man has not had proof by biopsy, although I think that he falls into the same category. His stools are of normal color. He has no other evidence of extrahepatic obstruction.

These cases are presented from the standpoint of being interesting to the general practitioner because of the widespread systematic disease and to the dermatologist because of the striking dermatologic pictures which are the outstanding manifestations. The prognosis is poor in both the cases.

A Case for Diagnosis (Syphilitic Glossitis?). Presented by DR. JOHN G. DOWNING, Boston.

J. L., a 73 year old white man, has complained of a sore mouth and tongue for two years. This has been an intermittent disturbance of irregular occurrence. In 1942 he was found to have a positive reaction to a serologic test of the blood for syphilis.

The anterior portion of the tongue is distinctly atrophied. There are a few superficial ulcers along the sides. The buccal mucous membranes and the dorsum of the tongue are covered with patches of a grayish white exudate which is not easily removed.

A culture planted with material from the mouth has shown no growth of fungus.

Treatment has consisted of potassium iodide by mouth and a mouthwash of sodium perborate.

DISCUSSION

DR. JACOB H. SWARTZ: It seems to me that this man has a degenerative process superimposed on a syphilitic base.

DR. FRANCIS M. THURMON: There is an element of avitaminosis which is superimposed on a syphilitic background. When the left margin of the tongue was palpated, there was a certain amount of induration suggestive of an early

stage of a malignant growth. Submaxillary and submental glands were not palpable. Intraoral cancer, especially of the tongue, in a patient with tertiary syphilis does not respond to treatment. It usually requires six to nine months for the fatal outcome, despite any and all types of therapy used. A histologic examination of the lesion of the tongue should be made.

DR. JOSEPH MULLER: Suggestions for therapy were requested. I should say that there is definitely a possibility of a malignant growth, but the proper procedure would be to give him adequate antisyphilitic therapy and plenty of vitamins first and suspend decision on further steps until one sees if he has a cancer. Let the two things which are visible be treated.

DR. GEORGE E. MORRIS: There is a group of syphilologists who believe that a patient with a tongue such as this should not receive arsenotherapy. How do the members feel about this?

DR. FRANCIS M. THURMON: In the past two years I have seen 3 cases like this. Each has been fatal; each patient had intensive therapy for syphilis, and it accomplished nothing.

DR. WALTER T. GARFIELD: I can recall 2 similar cases: in the 1 the patient was a woman who had had syphilis years ago as a girl and had some treatment. Later a dentist discovered this condition in her mouth, and she was referred to me. A serologic test of the blood for syphilis elicited a positive reaction. I gave her the regular treatment of arsenic and bismuth compounds; the lesion on the tongue did not clear, but it did improve. She lived for ten or fifteen years longer; the last time I saw her she was 80 years old. In the other case the patient was a man whom I treated eight or ten years ago; he is still alive and active.

DR. FRANCIS M. THURMON: Did Dr. Garfield have biopsies done?

DR. WALTER T. GARFIELD: No.

DR. WILLIAM P. BOARDMAN: I thought that this was a case of leukoplakia, but there is certainly degeneration on the left side of the tongue. I recommend a histologic examination. Leukoplakia does not improve with antisyphilitic treatment.

DR. C. GUY LANE: One thing which impressed me is the fact that this man had potassium iodide for an unstated period without response. How long did he take it?

DR. BERNARD APPEL: It was not long, and the dose was not large—30 drops daily.

DR. C. GUY LANE: I should not think that a fair test on which to make any estimate of response to treatment. I feel that there is syphilis present. This impresses me as a manifestation of late syphilis, and I should give him an adequate trial with chemotherapy. I should be inclined to begin with potassium iodide and a bismuth compound or mercury. I should not hesitate to give him arsenic. I believe that a leukoplakic area should be examined histologically. The patient should have an adequate vitamin intake. A hunt for Monilia was made, but I think that nothing was found. The cultures were sterile.

DR. JOHN G. DOWNING: I saw this patient yesterday, and the members may be interested in the orders for treatment. I had my dental consultant see him also. He is being sent into the hospital, first to have the dental caries relieved, second, to undergo histologic study and third, to receive a full course of penicillin and large doses of vitamins. I think that the condition in this case is a combination of syphilis with secondary infection of the mouth; the latter may be moniliasis or infection with various pyogenic bacteria. I think that it could come from the carious teeth and the pyorrhea present. Then, with regard to the possibility of a malignant growth, I could not find any evidence of one yesterday. The leukoplakia may improve with this therapy. I do not agree with Dr. Thurmon. I think that a man who has had this for two years may improve a great deal. I have seen this type of leukoplakia last for many years.

DR. AUSTIN W. CHEEVER: Dr. Downing has explained this whole situation extremely well. I do not see any evidence of cancer. It might easily be there or eventually develop. I do not think that anything can be accomplished by anti-syphilitic treatment. I have seen patients with tongues like this who lived for years. I have no objection to giving him treatment, but I should keep it within cautious and reasonable limits.

DR. EDWARD A. LAFRENIERE: When this man was first seen, about a month ago, he was worse than he is now; the diagnosis was vitamin B deficiency. He was given prescriptions for potassium iodide and sodium perborate. The following week he came back worse, and all the prescriptions were in his pocket. The next week he returned with some improvement after taking vitamin B complex. Material was taken for microscopic examination and culture at that time. I definitely saw some filaments of fungi in the smear. Since then the picture has not changed appreciably.

A Case for Diagnosis (Tuberculosis Orificialis?). Presented by DR. BERNARD APPEL, Lynn, Mass.

M. M., a 25 year old American Negro woman, first noticed a growth near the anus three months ago. It was mistaken for a hemorrhoid. The lesion continued to enlarge and about three weeks ago became painful.

There are two extremely tender irregular ulcers of the perineum. They extend from the frenulum pudendi posteriorly to the anus and beyond for a short distance, forming a ragged ulcerated area approximately 8 cm. by 6 cm. The edges are firm and somewhat undermined in some places and granulomatous in others. From the ulcer on the left of the anus are two fistulas, one leading into the rectum and the other into the vagina. They are difficult to probe and are extremely tender.

The Frei test for lymphogranuloma venereum gave negative results. A roentgenogram showed that the chest was normal. The Volmer tuberculin patch test elicited a negative reaction. The Hinton, Wassermann and Kahn reactions of the blood were positive. Histologically, this lesion resembled granuloma inguinale, but no leishmania bodies could be demonstrated.

No treatment has been instituted.

DISCUSSION

DR. MAURICE J. STRAUSS: I could not find the slide, but the case report stated that the biopsy had been reported as being consistent with a diagnosis of granuloma inguinale, although no leishmania bodies were found. It is not always easy to find leishmania bodies. In fact, in a large percentage of cases it is impossible, and I do not feel that this rules out the diagnosis of granuloma inguinale.

DR. BERNARD APPEL: While making the rounds of the wards a few days ago I asked Dr. John Foley, who has had experience with tuberculosis, to examine this patient. He did so and expressed the opinion that this entire picture was consistent with tuberculous ulcer because of its location, the undermined edges of the ulcer and the entire clinical picture. Dr. Foley said that he has seen many of these perianal tuberculous ulcers and that this case fits in with the picture.

DR. MAURICE J. STRAUSS: It may be of interest to know that when I looked at this patient there was no history of the case available and that one of the possibilities that occurred to me was that this might be tuberculosis. I also want to point out that these granulomatous lesions around the anal orifice are most difficult ones on which to make an accurate diagnosis. Some of them will show a microscopic picture consistent with tuberculosis and will later on be found to be a foreign body reaction. In this particular case there is no evidence that the biopsy showed a picture which looked like either tuberculosis or a foreign body reaction; so I believe that one must be satisfied with the diagnosis of granuloma inguinale.

DR. WALTER T. GARFIELD: For my own information, I should like to know how often one finds these tuberculous ulcers around the anus without other tuberculosis. The patients whom I have seen have had tuberculosis above the ulcer. I have not seen any with a normal chest, a negative reaction to tuberculin and no history of tuberculosis at all.

NOTE.—Another biopsy report of an examination made about four weeks after the meeting at which the case was presented stated that the condition was consistent with lymphogranuloma venereum. Also, persistent questioning brought out a history of ten months of antisyphilitic treatment and a previous positive culture for gonococci. After treatment with 2,800,000 units of penicillin by intramuscular injection of 40,000 unit doses at three hour intervals, there was a dramatic healing of the entire ulcerated area. The two fistulas are still patent.

A Case for Diagnosis (Multiple Idiopathic Hemorrhagic Sarcoma or Hemangioendothelioblastoma?). Presented by DR. JOHN G. DOWNING, Boston.

J. G., a 57 year old white man, noticed a small dark spot on the dorsum of the left foot seven weeks ago. About five weeks ago two smaller lesions appeared on the right hand and one on the left hand. There have been no subjective symptoms relative to these cutaneous lesions. He was subsequently admitted to the Boston City Hospital with the complaint of a cramplike, diffuse abdominal pain accompanied with nausea, vomiting, chills, fever and sweats.

An examination revealed only lesions of the hand at this time; the original one on the left foot has been removed for study. On the flexor aspect of the third and fifth fingers of the right hand there are lesions 0.5 to 1 cm. in diameter. These are slightly raised papules of purplish color. One similar lesion is present on the left palm and is surrounded by a red areola.

A histologic examination of the lesion taken from the left foot showed idiopathic hemorrhagic sarcoma of Kaposi. There was bile (3 plus) in the urine. The nonprotein nitrogen in the blood was 35 mg. per hundred cubic centimeters, and the serum protein level was 5 mg. per hundred cubic centimeters, with an icteric index of 12. The Hinton reaction of the blood was negative. A 2 plus reaction to the cephalin flocculation test was obtained. The Graham test showed faint filling of the dye in the gallbladder and 40 per cent emptying.

The patient has been on a fat-free diet, with symptomatic improvement.

DISCUSSION

DR. WALTER T. GARFIELD: I have known this man since perhaps 1921 or 1922. About two years ago he came into my office exhibiting a lesion on the foot which I thought was a hemorrhagic sarcoma of Kaposi. At that time he was attending the Massachusetts General Hospital for his arthritis, and I suggested that he show the staff the lesion and ask them to perform a biopsy. The next time he appeared, it had been removed by another physician. I think that it was probably burned out. No report was obtainable.

DR. JACOB H. SWARTZ: I favor the diagnosis of Kaposi's disease but should like to suggest also the diagnosis of melanoma. I have seen one or two lesions that were diagnosed as Kaposi's sarcoma, but which turned out to be melanoma.

DR. WALTER T. GARFIELD: One should recall that Kaposi's sarcoma is usually symmetric and bilateral. This man has had nothing on his other foot.

DR. JOHN G. DOWNING: Dr. Swartz's suggestion is excellent. From a medicolegal standpoint these cases are important. All dermatologists have a tremendous dread of removing pigmented moles. The small nodular lesions on this man's palms suggest systemic disease to me. A history of the removal of a small tumor and the later appearance of other lesions may incriminate the trauma, but one forgets that many of these conditions originate systemically. I am tempted to believe that this case is one of hemangioendothelioblastoma rather than of Kaposi's

disease. If the picture is studied histologically, sarcoma can definitely be disregarded. There is increased vascular tissue and little increase in fibrosis. In hemangioendothelioblastoma, the primary lesion may be in the liver. I think that this man should be studied with that in mind; he does present signs of hepatic disturbance.

Juvenile Acanthosis Nigricans and Ichthyosis. Presented by DR. LEON BABALIAN, Portland, Maine.

E. B., a 22 year old white man, presents a symmetric eruption involving the upper two thirds of the body, which began when he was 3 months old. It was said to be a "dirty-looking spot" when it was first seen. This spread steadily until it covered most of the trunk, the neck and the upper extremities. A few lesions appeared on the thighs when the patient was 6 years old, but they faded away several months later. When he was 12 years old, some appeared on the face. Since that time there has been no further change in the area of involvement, but the eruption has become progressively rougher, thicker and darker. The patient is said to have always been deficient physically and mentally. His mother has diabetes. She and one other offspring have several moles, but there is no familial history of any eruption similar to that exhibited by the patient.

The cutaneous surface is generally rough, dry and thick, is covered with numerous papillary growths and has a dirty brownish hue. Scattered over both cheeks are yellow-brown papules the size of millet seeds. They are larger on the eyelids, which are furrowed. The whole scalp is thick, rough and verrucous in appearance. On the neck the papillary growths become confluent, forming dark brown, thick patches with exaggeration of the folds of the skin. These areas are sprinkled with pea-sized nodules. Excepting these larger excrescences, the same kind of patches are seen on the torso. In places they form wide stripes with infrequent thin channels of normal skin between them. They are thicker and darker on the nipples and in the umbilical area. On the flexor surfaces of the upper extremities and the groins, the patches turn grayish black and pachydermic; with extension movements they appear to be formed of parallel horny ridges separated by deep rugae. On the front and back of the penis, there are longitudinal stripes of the same eruption. The mouth, hands, feet and legs appear normal. There is no change in the hair and nails.

A biopsy specimen taken from the neck showed a thickening of the epithelium. The basal layer was more prominent than usual, with excessive pigment. There was hyperkeratosis, and in places there were keratinized plugs with small epithelized cysts. In the corium there were occasional chromatophores filled with pigment. The papillae were hypertrophied, elongated and in some places divided. There was a mild lymphocytic infiltration in the corium.

A roentgenologic examination revealed that the gastrointestinal tract was normal. Results of the routine examinations of the blood and urine were within normal limits. The Hinton and Kahn reactions of the blood were negative.

For six weeks the patient has been taking 200,000 units of vitamin A daily. In that time his eruption has faded noticeably on the face and neck.

DISCUSSION

DR. FRANCIS M. THURMON: What faded in this case? The lesions are so extensive that improvement must have been minimal. From the history, some lesions apparently disappeared spontaneously before the administration of vitamin A.

DR. ALFRED HOLLANDER: Clinically, this case does not appear to me as one of juvenile acanthosis with ichthyosis. In the latter disease there should be more hyperkeratotic lesions. I think that one should consider this a nevus because the pigmented areas on the abdomen undergo transition from smooth skin to a nevus verrucosus type of lesion. Histologically there is one section which looked typical of this diagnosis.

DR. WALTER F. LEVER: The histologic section did look like nevus verrucosus. I think that it makes little difference whether one uses the clinical designation nevus verrucosus or ichthyosis hystrix. I think that they are both nevoid and the same thing.

DR. FRANCESCO RONCHESE: Nevus verrucosus and ichthyosis hystrix should be considered identical.

DR. JACOB H. SWARTZ: I note that the diagnosis is juvenile acanthosis nigricans with ichthyosis. I think that acanthosis nigricans will cover the whole thing. First of all, the disease came on when the patient was 3 months old. He has definite hyperkeratosis on the nipples. The eruption came first on the neck, where acanthosis of the juvenile type frequently begins. It has the distribution of acanthosis nigricans. I should much prefer to call it juvenile acanthosis rather than ichthyosis.

DR. JOHN G. DOWNING: I disagree with Dr. Swartz. Ichthyosis hystrix is a dermatologic entity which merely resembles another in some respects. Juvenile acanthosis nigricans is a separate clinical entity. This eruption is a nevus which is verrucous and should be classified as ichthyosis hystrix. I think that the two entities should be kept distinct.

DR. LEON BABALIAN: I think that both these diagnoses are correct. The pigmentary and papillary growths scattered all over the body are, according to Darier's description, characteristic of acanthosis nigricans. On the other hand, the hyperkeratotic appearance of many of these areas and their linear disposition fit into the diagnosis of ichthyosis hystrix. The same uncertainties prevail in the pathologic picture, which is one of papillary and hyperkeratotic nevus, but with an abundant amount of pigment that is unusual in ichthyosis hystrix. In the literature the association of acanthosis nigricans with nevoid changes is not rare, and it is my belief that juvenile acanthosis nigricans and nevus are one and the same disease.

What also interested me was that this condition improved with large doses of vitamin A. I am aware that spontaneous remissions can be seen in acanthosis nigricans, but the rapidity of the improvement was surprising after this medication.

A Case for Diagnosis (Psoriasis; Dermatitis Medicamentosa?). Presented by DR. FRANCIS M. THURMON, Boston.

S. N., a 6 year old white girl, was presented with a generalized eruption of eight days' duration. Two weeks ago a small "pimple" appeared on the lateral aspect of the left leg. This enlarged to form a round, yellowish, crusted lesion 4 cm. in diameter. Eight days ago the eruption became generalized, and additional lesions have continued to appear. Six days ago sulfathiazole was prescribed; a total of 12 tablets was taken. A sulfathiazole ointment was applied two days ago to the area on the left leg. There has been no pruritus.

This eruption is a generalized dermatitis, including the scalp, palms and left sole. It is papulovesicular, with discrete lesions of 2 to 10 mm. in diameter. They rest on a red base, and some have acquired a yellowish crust, while others show fine white scales. On the forehead and cheeks and in the popliteal fossae, they have become confluent. There are no oral lesions. A few cervical and submaxillary glands are palpable.

The laboratory findings were as follows: The rapid Hinton reaction of the blood was negative. A urinalysis showed 0.1 per cent sugar, no acetone, no diacetic acid and no sediment. A routine examination of the blood gave results within normal limits except for a 10 per cent eosinophil count in the differential smear.

DISCUSSION

DR. JACOB H. SWARTZ: This patient interests me because I have had 2 similar ones in private practice, and I saw 1 or 2 at the Massachusetts General Hospital.

The eruption is psoriasis of the acute type, coming on within ten days after the patient had a sore throat and had received a sulfonamide compound. The diagnosis of psoriasis was confirmed pathologically. In each instance there was reason for giving the drug. Do sulfonamide compounds or infections of the upper part of the respiratory tract precipitate potential psoriasis? There have been too many such instances to be coincidental.

DR. ELLWOOD C. WEISE: That is a keen observation. I have noticed the same thing on 2 occasions, both eruptions occurring in children after a sort throat. In my patients typical guttate psoriasis developed. These cases occurred before the days of sulfonamide drugs; so the drugs could not be blamed. The development of acute psoriasis following an infection of the throat seems to me to be more than coincidental.

DR. ALFRED HOLLANDER: I have seen 2 cases of this kind. In the first case the patient showed a generalized psoriasis after sulfathiazole was given internally for sore throat, and in the second the eruption developed into generalized psoriasis after an application of sulfathiazole ointment. In the latter case the patient had injured his leg; the resulting abrasion was treated with 5 per cent sulfathiazole ointment. He struck his leg again fourteen days later; psoriasis developed on the site of the injury and became generalized after another two weeks.

DR. LEONARD E. ANDERSON: I recall 2 specific instances in which there occurred rapidly developing guttate psoriasis following an illness with fever when no sulfonamide drug had been used.

DR. AUSTIN W. CHEEVER: I remember 1 patient who had psoriatic papules everywhere that chickenpox lesions had been. In another patient psoriasis developed in subsiding syphilitic lesions. I have seen 2 instances in which psoriasis appeared around or in the scar from vaccination.

DR. ELLWOOD C. WEISE: In this particular case there were no previous cutaneous lesions. The incidents which Dr. Cheever and Dr. Hollander presented are well known, namely, that previous injury or some change in the skin will determine the localization of the psoriatic lesion. However, in this particular instance there were no previous cutaneous lesions prior to the onset of the sore throat.

DR. AUSTIN W. CHEEVER: I saw 1 girl who had two attacks of psoriasis, twelve years apart, each coming on after tonsillitis before the days of sulfonamide drugs.

DR. FRANCIS M. THURMON: I have always looked on these cases of acute psoriasis as being due not to an acquired factor but rather to the blending of the chromosomes which denote the biologic habitat of each person. Whatever the stimulating factor is, be it drug or trauma or excessive amounts of sunshine, the cutaneous response of psoriasis is always the same. That is what happened in this case; namely, a stimulus played on a certain type of physiologic background, and the response was psoriasis.

DR. ALFRED HOLLANDER: I believe that this case can be explained by the theory of Koebner's phenomenon.

Tertiary Syphilis of the Skin. Presented by DR. G. MARSHALL CRAWFORD, Brookline, Mass.

A. L., a 49 year old white man, complained of a dry, cracking eruption of the left palm of six years' duration. There have been occasional episodes of bleeding from the area. The eruption gradually spread over the wrist, with the development of red scaly lesions. About a year ago these appeared on the back of the hand. The patient is a cattle dealer, and his hand is subject to considerable trauma. There is no other history of cutaneous disease. The patient said that he had no venereal infection. The marital and general medical histories were noncontributory.

Tests of the blood have been made repeatedly in the past and are said to have given normal results. Several years ago the patient's family physician gave him eight injections into a vein of his arm; the nature of this treatment is not known. There was no improvement in his hand following this therapy.

The left hand reveals diffuse keratosis of the entire palm and the flexor aspects of the fingers; thickening is most pronounced on the palm. There is some fissuring in the flexural folds of the fingers. The keratotic change is rather well defined at the sides of the hands and the fingers. Proximally it thins out at the wrist into an erythematous, slightly scaly band about 4 cm. in width. The border of this zone is comprised of dull red scaly papules. The latter extend around the sides of the wrist and over the dorsum and are irregularly scattered over the back of the hand. There are moderate dryness and scaling but little or no thickening. A general physical examination revealed ptosis of the left upper eyelid. The blood pressure is 150 systolic and 100 diastolic. A neurologic examination revealed normal conditions. There are no other noteworthy observations.

Biopsy of a specimen from the left wrist revealed only chronic inflammatory changes. The Hinton and Wassermann reactions of the blood were positive.

DISCUSSION

DR. JACOB H. SWARTZ: The border is not nodular, although it is elevated. Has infection by Trichophyton rubrum been ruled out?

DR. G. MARSHALL CRAWFORD: I do not think that possibility was discussed. The diagnosis was made clinically before the pathologic report was returned. When one looks at the section after the report of a positive serologic reaction, the interpretation is apt to be colored, but I could not have made a diagnosis of syphilis histologically. I should like to have Dr. Lever's opinion.

DR. WALTER F. LEVER: The section did not suggest syphilis, because the vascular changes were not characteristic and there were few plasma cells. In most cases of secondary and early tertiary syphilis it is difficult to make a definite diagnosis on histologic grounds, and I believe that clinical means are more reliable.

A Case for Diagnosis (Dermatitis Medicamentosa?). Presented by DR. JOHN ADAMS JR., Boston.

S. B., a 67 year old white man of Italian descent, was admitted to the dermatologic ward of the Massachusetts General Hospital in February 1945. Six months previously, "blisters" had appeared on the left wrist, which were attributed to the leather strap of his wrist watch. The eruption became more pronounced and gradually spread to involve the whole body. A profusion of local applications had been used before the patient was admitted to the hospital, and some of these were felt to have been aggravating.

At the time of hospitalization there was a generalized dry, erythematosquamous dermatitis with extensive excoriation. Some areas were lichenified. There was moderate edema of the legs. A biopsy on admission revealed no diagnostic abnormality. Except for a white cell count of 10,000 and 27 per cent eosinophils in the differential smear, the results of the routine hematologic examination and the blood chemistry were within normal limits. The dermatitis became progressively worse, with the development of vesicles and bullae, especially on the legs. A pigmentary change began about this time and the entire skin has become steadily darker. A month after admission he contracted an acute pulmonary infection, which was treated with sulfadiazine. After this infection his renal function failed. On March 23 the nonprotein nitrogen content of the blood was 126 mg. per hundred cubic centimeters. It has slowly dropped to 75 mg. per hundred cubic centimeters at the last reading. There is albumin (4 plus) in the urine.

As seen today, this man presents a generalized pigmentation of dark brown, with a mottling of almost black pigment on the extremities. The legs, the volar

aspects of the wrists and the temples show numerous scars of 0.5 to 1 cm. in diameter with complete depigmentation. This change is most pronounced on the ankles, where a few partially dried bullae are interspersed among the scars.

DISCUSSION

DR. JOHN G. DOWNING: My diagnosis is dermatitis medicamentosa, probably due to the sulfadiazine.

DR. JACOB H. SWARTZ: I followed this patient while he was in the ward and before he was presented by Dr. Adams and I questioned whether or not the disease was a drug eruption. The blood sulfonamide level was determined ten days after sulfadiazine was administered, and the report was 2.6 mg. per hundred cubic centimeters. I think that the eruption is dermatitis medicamentosa.

DR. FRANCIS M. THURMON: When there is retention of one of the sulfonamide compounds over such a prolonged period, is there no way of elimination except by forcing fluids?

DR. GEORGE E. MORRIS: That is the way to get rid of it.

DR. CHARLES W. O'NEILL: I have a theory in regard to neutralizing sulfonamide compounds. The vitamins are destroyed by these compounds; by the same token, could they be destroyed with large doses of vitamins?

DR. JACOB H. SWARTZ: Paraaminobenzoic acid is supposed to inactivate sulfonamide compounds. Why not try it on this patient?

DR. GEORGE E. MORRIS: It should be pointed out that some of the vitamins interfere with the ability of the bacteria to react to the sulfonamide drugs. There is absolutely no chemical reaction between the vitamin and the sulfonamide derivative; thus, there can be no destruction, inactivation or increased secretion because of the intake of vitamins.

DR. C. GUY LANE: It has been my opinion that the disease in this case is more consistent with lichen planus bullosa than with a drug eruption. It seems to me that when I first observed this man he had lesions on his arms which were certainly lichenoid in character. I do not remember that I saw any real striae, and the papules were not all exactly angular, but they fitted into the picture of lichen planus rather than into that of a drug eruption. Scratched papules in many instances can become lichenoid in character. The development of new bullae such as the large one seen today certainly should not occur unless the patient has had more of a sulfonamide compound, and he has had none. I do not know whether a later sulfonamide level has been obtained. Lichen planus of the bullous type is unusual, but it seems to me that this diagnosis fits this case better than a drug eruption, although I realize that the nonprotein nitrogen level could be explained by a reaction to a sulfonamide compound better than by lichen planus.

A Case for Diagnosis (Dermatitis Herpetiformis or Pemphigus?). Presented by DR. F. RONCHESE, Providence, R. I.

G. F., a 24 year old white woman, was presented with a generalized eruption of about a year's duration. The onset was marked by pruritic bullae which apparently arose from normal skin and ruptured soon after their appearance. There has been no improvement from the use of numerous forms of topical therapy. Sulfapyridine was given orally for many months, without notable effect, and the eruption has grown progressively worse.

Scattered practically all over the body are moderate numbers of thin-walled, impetigo-like bullae, 1 to 2 cm. in diameter. They contain clear fluid, have no inflammatory halo and rupture with the slightest trauma. Many have been replaced by straw-colored crusts.

The results of the routine examination of the blood and the urine were within normal limits. The fluid contents of the bullae were sterile on culture. The result

of the phytopharmacologic test of Pels and Macht was reported as 59 per cent (normal 70 to 75 per cent). The Wassermann reaction of the blood was negative.

DISCUSSION

DR. JACOB H. SWARTZ: I should like to suggest the Senear-Usher syndrome for consideration. The patient has lesions over the nose and a positive Nikolsky sign, which go with this syndrome.

DR. JOHN G. DOWNING: Darier mentioned a bullous eruption which is called *pemphigus hysterique*, occurring in young females (Darier, J.: Précis de dermatologie, Paris, Masson et Cie, 1923, p. 222).

DR. WALTER F. LEVER: I agree with the diagnosis of Senear-Usher pemphigus. The good general condition of the patient and the duration of her disease are not at variance with this diagnosis.

METROPOLITAN DERMATOLOGICAL SOCIETY

Royal M. Montgomery, M.D., *President*

James Lowry Miller, M.D., *Secretary*

April 16, 1945

Dermatitis Venenata. Presented by DR. ROYAL M. MONTGOMERY.

E. M., a white woman aged 46, has had a dermatitis of some part of her body for over ten years. The eruption started on the palms ten years ago. Two years ago, following roentgen therapy to the palms, the eruption spread to the arms, legs and feet. When first seen, seven months ago, she had scattered papules on the neck and arms. There was maceration on and between the toes.

At present, there is dermatitis of the face, eyelids and neck. There is mild dermatitis of the arms and hands, which she keeps covered with a paste of zinc oxide and starch. The feet are free from maceration between the toes. The Wassermann reaction of the blood was negative. An examination revealed no tinea between the toes. The result of a patch test with paraphenylenediamine (2 per cent) was negative.

In June 1939, the results of patch tests made elsewhere with oil of orange, crude coal tar, Coty's perfume, Macy's shoe polish, Johnson's floor wax, Stafford's silver polish, powder and benzine were positive.

DISCUSSION

DR. RICHARD J. KELLY: I favor the diagnosis of dermatitis venenata. I think that the patient deserves a fair investigation, and I suggest that she get the most bland treatment at the present time.

DR. MAURICE J. COSTELLO: This patient has contact dermatitis with eczematous features. I am sure that the dermatologists who have seen her have had trouble finding the cause of her eruption. Some one might come on it accidentally rather than find it by the usual thoroughgoing methods. The patient stated that when she goes away for the summer the eruption improves, only to recur after she returns.

DR. ROYAL M. MONTGOMERY: This patient presents a problem in that she neglects to carry out my suggestions for treatment. She has been to different dermatologists while she has been under my care. This causes confusion in her mind. I believe that she should be hospitalized, use only the preparation prescribed and be given patch tests to find out the sensitizing agents.

Giant Urticaria with Lymphedema. Presented by DR. LESLIE P. BARKER.

A. B., aged 20, was first seen on March 22, 1945, at which time she gave a history of swelling of the nose, upper eyelids and cheeks for a period of two

years. While she was away at school two years ago, she woke up one morning with her eyelids and nose tremendously swollen, without redness, pain or fever. The acute part of the edema subsided within twenty-four hours, but since that time the swelling of the nose and, to a less extent, of the eyelids has never entirely subsided. She has had rather frequent attacks of the acute swelling during the two years. She is certain that any foods containing wheat products cause an attack. Otherwise, she has no idea of any etiologic factor.

She has had hay fever since childhood. Her father also has had hay fever. One grandmother had asthma. Her hay fever has been produced by dust and air-borne pollens. An examination and roentgenograms of the sinuses showed no involvement.

There is a firm, rubbery edema of the entire nose, especially over the bridge, and a moderate amount of edema of the eyelids. There is neither discoloration of the skin nor sign of inflammation. A recent thorough study by an allergist, which included tests with foods, air-borne pollens, fungi, and bacteria cultured from the nose, nasopharynx and throat, showed the following positive results: Strongly positive reactions were obtained from grasses, especially ragweed, and also dust and feathers. Moderately positive intradermal reactions were given to Streptococcus viridans obtained from the nose and throat. The results of intradermal scratch tests and patch tests with wheat were all negative.

DISCUSSION

DR. MAURICE J. COSTELLO: From time to time at the dermatologic societies similar cases have been presented in which there has been involvement of the eyes, nose, cheeks and lips, and less frequently of the ears and genital region. The best results in my experience and in the experience of others have been obtained from the administration of sulfonamide drugs, especially sulfapyridine, which is the most effective of the sulfonamide compounds. One would risk less by giving the patient a trial treatment with penicillin, 25,000 units being administered every three hours for two weeks and possibly longer.

DR. J. LOWRY MILLER: I believe that by now chronic lymphangitis is present. For this reason a trial treatment with penicillin is indicated, as the results in some cases have been excellent. Larger doses of penicillin over a shorter time are to be preferred to smaller doses over a longer time.

DR. THOMAS N. GRAHAM: I agree with Dr. Miller that it is advisable to start with larger doses and to discontinue the use of medicament after three or four days if there is no improvement.

DR. W. SODA (by invitation): I have treated a number of patients with penicillin for a period of one to two weeks. In my experience at Bellevue Hospital one or two weeks is required for definite improvement to be noticeable.

DR. RICHARD J. KELLY: I agree entirely with Dr. Costello—that is, sulfonamide compounds or penicillin should be used, but in concentrated doses. I think that the woman has lymphangitis of the erysipelatous type.

DR. ROYAL M. MONTGOMERY: This condition should be diagnosed as lymphedema. I am in agreement with the opinions of the other men about sulfonamide drugs and penicillin. I think that it should be pointed out, as Dr. Soda has said, that the results occur not in a few days but in a few weeks with the medicaments mentioned.

DR. LESLIE P. BARKER: The history that the eruption subsides slightly but never completely makes me feel that, although she may have had giant urticaria initially, there is a great deal of chronic lymphedema present at this time that may be permanent.

The case has been presented for suggestions as to treatment. I wonder if any one has had experience with radiotherapy in these cases. One patient at Vanderbilt Clinic with lymphedema of the upper lip improved with sulfonamide drugs and

filtered roentgen ray therapy. I have hesitated to give radiotherapy in this case because of the possible danger to the visual nerve (optic nerve).

A Case for Diagnosis (Bowen's Disease? Tuberculosis Cutis?). Presented by DR. THOMAS N. GRAHAM.

W. R., a white man aged 42, was first seen by me on March 7, 1945. He complained of an eruption of approximately twenty years' duration on the left hand. He stated that the eruption had started as a small raised patch, which gradually spread peripherally to its present size. He was treated a year ago with fractional roentgen ray therapy, with no improvement. His occupation for the past two years has been clerical, and previously his work consisted of handling raw meat. There has been no pruritus.

An examination showed an irregular erythematous scaly patch 4 by 5 cm. in diameter The margin is moderately indurated. In the center of the patch is a verrucous area. There is some superimposed crusting on the remainder of the patch. Adjacent to the verrucous area there is a scar, the site of a lesion which was removed with a cautery a number of years ago.

A biopsy specimen showed the epidermis to be acanthotic, with a nonparakeratotic scale and with well defined rete pegs. Many of the prickle cells contained large and hyperchromatic nuclei as well as mitotic figures. There was a zone of inflammatory exudate in the corium. The histologic picture was consistent with but not definitely diagnostic of Bowen's disease.

DISCUSSION

DR. J. LOWRY MILLER: I believe that the man has keratoses of the palm and the soles which are characteristic of those caused by arsenic. The lesion on the back of the hand is a Bowen type of epithelioma, which has been seen frequently arising in patients who have taken arsenic over a long period.

DR. LESLIE P. BARKER: In view of the pluglike keratoses of the palm and the soles, I think that this patient definitely has arsenical keratoses. The irregular erythematous scaly patch on the hand I think is Bowen's type of precancerous lesion. The blood should be tested for the presence of arsenic, and if there is no arsenic the patient should have several doses of sodium thiosulfate and a test of the blood for arsenic should be repeated. A biopsy of tissue from the lesions of the hand should be performed.

DR. RICHARD J. KELLY: I agree with the previous speakers. I think that the patient definitely has arsenical keratoses. I am in disagreement with desiccation as a method of treatment. I think that the patient should be given thorough fractional roentgen ray therapy by the Coutard method. The lesion probably would entirely disappear with this type of therapy. I agree with Dr. Barker that the patient should be tested for the presence of arsenic.

DR. MAURICE J. COSTELLO: I agree with the diagnosis of arsenical keratoses. The lesions are typical. The point that Dr. Fox made about arsenical keratoses is that the lesions are often on the sides of the hands and the sides of the fingers. The large lesion could easily be mistaken for tuberculosis verrucosa cutis. I am under the impression that the lesion would not respond to roentgen rays. I think that it would be simple to inject a solution of procaine hydrochloride into the lesion and destroy it by surgical diathermy.

DR. ROYAL M. MONTGOMERY: I believe that this man has Bowen's disease superimposed on or caused by arsenical keratoses. A similar case was presented by me before this society four years ago (ARCH. DERMAT. & SYPH. **45**:407 [Feb.] 1942). I have encountered a half dozen other cases since then. Desiccation and curettage of lesions of the Bowen type are the best method of treatment. Arsenical keratoses are difficult to cure.

DR. THOMAS N. GRAHAM: I agree that this is probably a case of Bowen's disease superimposed on arsenical keratoses.

Hydroa Vacciniforme (Hydroa Aestivale). Presented by DR. J. LOWRY MILLER.

F. S., a girl aged 14, was first seen at Vanderbilt Clinic in September 1944. She complained of red vesicular lesions which have appeared on the hands since she was 1 month of age after even slight exposure to sunlight. In the winter no lesions have been present. In the summer, during the hot weather she perspires little, but she has never collapsed from the heat. The mother has noticed that she does not perspire as do the other members of the family. The patient has been free of all lesions during this past winter. Two weeks ago, a few lesions again appeared on the face.

An examination showed a few pea-sized red scaling areas at the sites of dried-up vesicles. These lesions are present on the nose and cheeks. A complete blood cell count showed normal conditions. The blood cholesterol level was 179 mg. per hundred cubic centimeters. The basal metabolic rate was + 10 per cent.

Treatment has consisted of injections of solution of liver intramuscularly and administration of vitamin B complex by mouth.

DISCUSSION

DR. THOMAS N. GRAHAM: Patients with hydroa vacciniforme present definite scarring from previous lesions, but I did not see scarring in this patient. One of the diagnostic features is scarring from previous lesions, with the appearance of bullae and vesicles during the summer when the areas are exposed to the sun. I am unable to suggest a diagnosis in this case.

DR. W. SODA (by invitation): I think as Dr. Graham does. The patient has a history of recurring lesions. On inspection there did not seem to be evidence of much scarring.

DR. RICHARD J. KELLY: I suggest that she has dermatitis herpetiformis in one form or another which could be interpreted as hydroa vacciniforme. I prefer the diagnosis of dermatitis herpetiformis.

DR. MAURICE J. COSTELLO: As Dr. Graham mentioned, I do not see the rather conspicuous scarring that should follow or be part of the picture of hydroa vacciniforme. One had to look closely for a few areas of depigmentation and superficial scarring. I think it is barely possible that this patient has had prurigo hiemalis appearing on the extensor surfaces of the extremities. I suggest that the child be exposed to sunlight for increasing periods and be given an ointment which would make the skin somewhat impervious to sunlight.

DR. LESLIE P. BARKER: The location of this eruption on the cheeks and the arms, consisting of a few pea-sized crusted areas, suggests hydroa vacciniforme, but the lack of scarring is certainly against that diagnosis.

DR. J. LOWRY MILLER: I saw the patient last fall, at which time there were bullous lesions involving the arms and the face limited to the areas exposed to sunlight. Similar lesions have been present since the patient was 1 month of age, appearing each spring and clearing in the early fall. I believe that there is no question that this is a case of sensitivity to light, a mild hydroa vacciniforme. The child was underweight and run down. She was given injections of liver substance. She gained weight and appears physically much better. No lesions have been present all winter. With the approach of spring, the lesions began to appear on the nose, which is the first location involved each year. The child has been given ultraviolet irradiation but is not able to build up sufficient resistance to prevent lesions on exposure to sunlight. The mother is an intelligent woman, and I believe that she is forced to keep the child out of the sun.

NOTE.—Sections of cutaneous tissue disclosed a moderate hyperkeratosis and a slight acanthosis, with individual epithelial cells being hydropic. The cutis appeared to be somewhat edematous, with slightly dilated capillaries and minimal perivascular infiltration.

Syringocystadenoma. Presented by Dr. J. Lowry Miller.

M. M., a Puerto Rican aged 23, was admitted to the New York City Hospital clinic on April 9, 1945, complaining of lesions of the eyelids and the "V" of the neck which have been present for the past five years. She has never had any treatment.

An examination showed about a dozen discrete pinhead-sized to split pea-sized round, smooth nodules which are somewhat brownish to yellow. Similar lesions are situated on the "V" of the neck. No laboratory reports have been received as yet.

DISCUSSION

Dr. W. Soda (by invitation): The small round sharply defined lesions seemed to fit definitely with my concept of a disease involving the sudoriferous glands. I agree with the diagnosis of syringocystadenoma.

Dr. Leslie P. Barker: I agree with the diagnosis of syringocystadenoma. Patients with this disease are resistant to treatment, and I should like to know whether any of the physicians have had any experience with light electrodesiccation. I have tried it in several cases, but there is some scarring produced and the lesions are not eliminated; also, new lesions continue to appear.

Dr. Richard J. Kelly: I agree with the diagnosis. As far as Dr. Barker's question is concerned, I do not think that roentgen rays would help.

Dr. Maurice J. Costello: The patient has multiple benign cystic epitheliomas. My idea of syringocystadenoma is that it is a disease which is confined to the chest, back and abdomen. I have never seen it on the face. If treatment is necessary and the lesions prove to be multiple benign cystic epitheliomas, I have treated them successfully with electric cautery.

I suggest that you perform a biopsy on specimens from two places, one from the eyelids and the other from the chest.

Dr. J. Lowry Miller: Biopsy would of course have to be performed to determine the diagnosis between multiple benign cyst and syringocystadenoma.

Note.—Biopsy sections taken from both the neck and the eyelid were diagnosed as syringocystadenoma.

A Case for Diagnosis. Presented by Dr. Maurice J. Costello and Dr. W. Soda.

J. O., a 54 year old Polish man, was admitted to Bellevue Hospital on March 20, 1945. About fifteen months previously, purpuric lesions had developed on both feet and legs. Since then these lesions have had a tendency to recur, in the afternoon especially. About ten months ago, he noticed several small growths on both ankles. These continued to increase gradually in size. He noticed no pain or particular discomfort. Two months later lesions of the same type developed on both knees. Since he has had these growths, the purpuric lesions have been more prominent. His past history revealed that a nasal polypectomy had been performed.

Multiple discrete, small, erythematous, macular lesions are present on the legs and the dorsa of the feet. There are also multiple, pale pink, sharply circumscribed, smooth-topped nodules, the size of hazelnuts and even larger, involving the lateral aspect of the left ankle and the calcaneal area of both ankles and also the anterior surface of both knees. Along the lateral border of the right foot are seen and felt two firm, diffuse, slightly elevated nodules. On the thenar eminence of the left palm is also seen a circular, smooth, diffuse, elevated nodule with a depressed center. There are varicosities of both legs with brownish pigmentation. The patient has bilateral chronic dacrocystitis, bilateral cervical adenopathy, partial occlusion of the nasal vestibules and two nodular prominences at the head of the left radius. The urine was normal. The blood was essentially normal except for mild leukocytosis. The Wassermann reaction was negative. The blood cholesterol level was 182 mg. per hundred cubic centimeters and that of cholesterol esters 100 mg. per hundred cubic centimeters. Tuberculin in a 1:100,000 dilution elicited

a 1 plus reaction and in a 1:10,000 dilution a 4 plus reaction. A roentgenogram of the elbows showed minimal hypertrophic changes.

DISCUSSION

DR. LESLIE P. BARKER: The lesion on the hand clinically certainly resembles granuloma annulare. It has a raised, grayish, firm, nodular border, and a biopsy specimen should be taken for a positive diagnosis. The nodular lesions around the elbow resemble clinically those of fibroxanthoma or juxta-articular nodules of syphilis. These lesions, however, cannot be reconciled with the hemorrhagic lesions on the legs.

DR. RICHARD J. KELLY: Further blood cell counts should be made. The serologic reaction should be rechecked. The cholesterol content is within normal limits. There is no history of diabetes, nor is there a history of arthritis. I think that the man has, as Dr. Barker suggested, a possible disturbance of the cholesterol, which is apparent on the skin. He said that he has never had leprosy. He does not have a leonine face, and his general condition seems good. If I had to make a diagnosis without further information, I should favor a disturbance of the cholesterol manifest in the skin, with possible cutaneous sarcoma.

DR. J. LOWRY MILLER: Without histologic diagnosis I should guess that the patient had some form of tuberculosis. The lesion of the palm looks like granuloma annulare. The other lesions resemble either xanthomas or a sarcoma type of eruption. If I had to put it in one classification, I should say sarcoma.

DR. THOMAS N. GRAHAM: I believe the lesions on the heels to be typical of xanthoma tuberosum multiplex. The lesions on the hands do not impress me as granuloma annulare. I think that biopsy of the lesions of the feet and the hands is necessary in order to establish a diagnosis.

DR. ROYAL M. MONTGOMERY: If I had to make a diagnosis, I should favor the diagnosis of some type of sarcoma. The nodules on the ankles and the knees and also the enlarged cervical glands should all fit into one diagnosis.

DR. MAURICE J. COSTELLO: If I had shown this patient tonight after I had given the microscopic diagnosis, there would have been no discussion. This patient was observed at Bellevue Hospital for six weeks. The results of biopsy suggest Kaposi's sarcoma, although to my mind the clinical picture is not that of Kaposi's sarcoma.

DR. W. SODA (by invitation): As Dr. Costello said the biopsy sections go to the general pathologic department, and often when there is any doubt the sections are taken to other pathologists in the city. It took approximately three and a half weeks for the report to be returned. A diagnosis of Kaposi's sarcoma was offered. As far as I am concerned, it is correct.

BROOKLYN DERMATOLOGICAL SOCIETY

David M. Davidson, M.D., *President*

Seymour H. Silvers, M.D., *Secretary*

April 23, 1945

Sarcoidosis. Presented by DR. NATHAN PENSKY.

J. A., a Negro aged 28, is presented with a history of an eruption which first appeared on the arm in 1941. In 1943 lesions appeared on the face. In 1944 a cough and shortness of breath developed. The patient was born in North Carolina. There is no history of familial pulmonary disease.

The patient now presents dusky red nodules on the forehead, eyelids, sides of the nose, ears, arms and backs of the hands. The lesions vary in size from that

of a split pea to that of a large bean. In addition, there is a bilateral tenosynovitis of the wrists, which superficially appears like a simple ganglion. Generalized adenopathy is present.

Tuberculin in a dilution of 1 : 100 elicited a positive reaction. A roentgenogram showed a fine nodulation throughout both lungs, with some hilar enlargement bilaterally, a widening of the superior mediastinum, which was probably due to paratracheal lymphadenopathy, and multiple thin-walled giant bullae in the right lung. The impression was that of sarcoidosis with bullous emphysema. Roentgenologic studies of the bones of the hands revealed small cystlike formations at several phalanges and similar lesions in several carpal bones, due to sarcoid infiltration. A histologic section was diagnosed as sarcoid.

DISCUSSION

DR. E. ALMORE GAUVAIN: I agree with the diagnosis. The value of a test with tuberculin in a 1 : 100 dilution is practically nil, since some degree of reaction can be obtained in almost any one with this concentration. One should use about a 1 : 100,000 dilution.

DR. JOEL SCHWEIG: I want to ask Dr. Pensky whether therapy has as yet been instituted. I believe that one is dealing with a special type of sarcoidosis in this case, as is seen in the American Negro and described by Klauder and Weidman. The clinical manifestations are characteristic—cherry-sized nodules are scattered over the trunk and the face. Klauder and Weidman believe that such eruptions are a sarcoid-like manifestation of tuberculosis of the skin. They find a positive tuberculin reaction as a rule. I suggest, therefore, further study with that in mind and also a determination of the albumin-globulin ratio in the blood, which is pathognomonic.

DR. NATHAN PENSKY: There is sufficient evidence to rule out the diagnosis of leprosy. The peculiar and characteristic involvement of the lungs, hands, skin and lymphatic glands is that found in sarcoidosis and not in leprosy. Tubercle bacilli have never been found in the sputum or by gastric extraction.

Up to the present time no therapy of definite value has been discovered. In some cases the cutaneous lesions resolve spontaneously; in others, progression continues in spite of treatment. A considerable number of patients suffering with this disease contract, and die from, generalized tuberculosis. The possibility should be borne in mind that these persons, having been hospitalized at an institution for patients with tuberculosis at some time during their life, may have contracted tuberculosis. One must remember that roentgenograms of the pulmonary fields resemble extensive tuberculosis and that often hospitalization as well as prolonged study is necessary to rule out tuberculosis.

There are several important points concerning sarcoidosis that should be stressed. Only one third of the patients with this disease present cutaneous lesions. About half the patients with progressive tuberculosis eventually die of the disease. Some competent investigators have found that in animals inoculated with tissue obtained from patients who have sarcoidosis tuberculosis develops on one or two passages. The association of this disease with the involvement of the reticuloendothelial system as well as the termination of many of these cases due to tuberculosis is more than coincidental.

Tinea Barbae. Presented by DR. SEYMOUR H. SILVERS.

J. B., a butcher aged 39, consulted me for boils of three weeks' duration on the face. He works exclusively at skinning calves, and he often brushes his face against the fur of the animals.

When he was first seen, four weeks ago, he had a hard, indurated red mass, the size of a small tangerine, peppered with pinhead white pustules, on the left side of the neck under the chin. Two smaller but similar masses, each the size of a large marble, were present on the right and left sides of the distal parts of the chin.

At present, the lesions on the chin are flat, red and devoid of hair. The lesion on the neck is red and indurated, with a few elevated papules. There are few hairs left in this area.

Repeated cultures of material from the infected areas did not produce a growth, and therefore the organism could not be identified.

DISCUSSION

DR. ABRAHAM WALZER: It is generally difficult to isolate the fungus. As a rule the eruptions respond to roentgen ray treatment.

DR. JACOB SKEER: Cases like this one are, to my mind, extremely uncommon. I saw 1 patient, an adult, with such an eruption in the bearded region. The lesions

Tinea barbae.

were somewhat smaller than those in the present cases, but more profuse, involving the chin, the lower jaw and the neck.

DR. SEYMOUR H. SILVERS: I have not seen a patient with tinea barbae for many years. This eruption is typical, and the diagnosis has been confirmed by direct examination of the hair. The patient skins approximately fifty calves a day and thus has ample opportunity to become infected. He has improved greatly within four weeks. He is receiving roentgen ray treatment, injections of trichophytin and manual epilation.

Prurigo Nodularis. Presented by DR. ABRAHAM WALZER.

R. W., a Negro aged 29, single, an ammunition handler by occupation, was first seen in the dermatologic clinic of the Jewish Hospital of Brooklyn two weeks ago. He gave a history of syphilis of a number of years' duration, and he had been treated at the Board of Health Clinic for the past four months. He had received about six intravenous and six intramuscular injections. The cutaneous

lesions for which he sought relief at this clinic had appeared two months ago, while he was receiving these injections. The Wassermann reaction of the blood was positive.

At present he shows lesions limited to the hands, fingers, forearms and backs of the elbows. These consist of many scattered, pea-sized or larger, raised, hard, smooth nodules. These are pruritic, as is evidenced by the scratched-off tops. Some of these are covered with thin scales or scabs, which on removal show a number of tiny, pinpoint openings.

DISCUSSION

DR. JACOB SKEER: The lesion appears to be a discrete nodule, about the size of a pea or smaller, with a superficial crust. Removal of the crust shows a little indentation, which may be necrosis or ulceration; this is not compatible with prurigo nodularis. These lesions are firm rounded nodules with a fine scale, which are intensely pruritic. They occur more on the lower than on the upper extremities, but they do occur on all the extremities and may occur on the face too. The lesions seen tonight suggested to me some type of papular necrotic tuberculid.

DR. JOEL SCHWEIG: I agree with Dr. Skeer. To my mind this is definitely not a case of prurigo nodularis. The location is not typical. The lesions do not present the characteristic nodular tumors, which would cause much more discomfort than the patient has. I believe that one is dealing in this case with keratoderma circumscriptum, possibly acquired in the course of the patient's work in a machine plant (not his regular occupation), and may belong in the group of industrial dermatoses.

DR. ABRAHAM WALZER: Prurigo nodularis usually occurs on the forearms, arms, thighs and legs, and also on the hands. The lesions in this case developed in the midst of syphilitic treatment and are therefore not likely to be those of syphilis. They appear to be a little too hard to be sarcoid. They are apparently too large for a papulonecrotic tuberculid. Therefore, to my mind, the only diagnosis that is possible is prurigo nodularis. The histologic studies may clear up the diagnosis.

Pseudopelade. Presented by DR. ABRAHAM WALZER.

K. C., a girl aged 14, was first seen at the dermatologic clinic of the Jewish Hospital of Brooklyn a few days ago. She gave a history of a bilateral mastoidectomy at the age of 8 years.

The present disease began about two years ago. The hair on the side of the head fell out suddenly and has never grown back. Examinations of the blood and the urine showed nothing abnormal. The Wassermann reaction of the blood was negative.

As presented, she shows an elongated area of alopecia, apparently composed of three joined, dime-sized patches. The central part is depressed, atrophic and faintly erythematous. The edge presents irregular indentations of tufts of hair.

DISCUSSION

DR. MORRIS M. ESTRIN: I think that this is a case of self-inflicted injury. Both the girl and her mother intimate that this is so. The girl said that she does not twirl her hair, but that sometimes she will pull at it and that she also rubs that area continuously. There is no atrophy to be seen, and I think that the patient's action is in keeping with trichotillomania.

DR. E. ALMORE GAUVAIN: I agree with Dr. Estrin.

DR. JACOB SKEER: The only thing against the diagnosis of trichotillomania is that the lesion is too well defined. I do not believe that that is the correct diagnosis, therefore. I also feel that there is a tendency to atrophy, and I agree with the diagnosis as presented.

DR. ABRAHAM WALZER: If these lesions were induced, the edge would not be so sharply demarcated. The floor would not be smooth and atrophic.

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

Harry C. Saunders, M.D., *Chairman*

Frank Vero, M.D., *Secretary*

May 1, 1945

Generalized Vitiligo: Alopecia of Undetermined Cause. Presented by DR. HELEN CURTH.

A. R., a Negro woman aged 40, is presented from the Vanderbilt Clinic with a generalized cutaneous disease of fourteen years' duration and alopecia of two months' duration. The patient was born with rather a dark skin, which remained that way until she was 26 years old. At that time her skin gradually began to turn white, first on the arms, trunk and legs and finally on the face. The entire skin stayed white with the exception of that of the scalp. Itching of the scalp and loss of hair started a couple of months ago. After the cutaneous lesions had begun, she received subcuaneous injections in the arms, given her by a private physician. The patient said that she had no "bad blood" or infections. Her skin began to turn dark again about four months ago.

At present, the patient's skin is for the most part white. She has symmetric islands of pigmented skin on her nose, cheeks, lips, chin, palms, soles and fingers. On the arms are seen small plaques of pigment. There are patches of alopecia on the frontal areas of the scalp, which otherwise appears normal. The hair is dark, with the exception of that on the sides, which is white.

A determination of arsenic in the blood is pending.

DISCUSSION

DR. CHARLES S. MILLER: This woman has never been a patient of mine, but I have seen her about town for the past fourteen years and have not observed any change.

Basal Cell Epithelioma of the Forearm. Presented by DR. JACK WOLF.

J. M., a man aged 64, was admitted to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital with a large lesion of five years' duration on the middle third of the right forearm. The lesion is irregularly rounded and sharply circumscribed and is about 3 inches (7.5 cm.) in diameter. The central area, of approximately the size of a 25 cent piece, is whitish, smooth and atrophic and surrounded by an erythematous, profusely crusted zone about ½ to ¾ inch (1.2 to 1.9 cm.) in width. At the periphery there is a fine, sinuous, raised, cordlike border.

A biopsy section from the peripheral zone confirmed the clinical diagnosis of basal cell epithelioma.

DISCUSSION

DR. CHARLES WOLF: In that location one would expect a squamous cell epithelioma or a prickle cell epithelioma.

DR. MAX SCHEER: When I first saw the patient, I thought that the lesion would probably be Bowen's disease, and I was surprised when the histologic report showed a pure basal cell epithelioma. Usually in these crusted lesions one expects to find a prickle cell epithelioma. In any event, according to my experience, basal cell epithelioma is rare on the extremities.

DR. EUGENE F. TRAUB: The center of a lesion of this type frequently heals as the active border spreads peripherally. In this case, the central scar was probably changed by factors other than treatment. Squamous cell lesions are encountered on the extremities much more frequently than are basal cell lesions, but I believe that the appearance in this case is suggestive not so much of a

squamous cell epithelioma as that of Bowen's disease, for which this lesion could have been mistaken.

DR. JACK WOLF: This is an excellent example of the banal basal cell epithelioma encountered so frequently on the extremities.

Multiple Keloids in Twin Sisters. Presented by DR. DAVID BLOOM.

E. M. G., a Negro woman aged 26, registered at the clinic of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on April 25, 1945, complaining of numerous cutaneous tumors of ten years' duration.

On the left and right arms, the right shoulder and the left knee there are firm tumors from the size of a walnut to that of an orange. On the sternum and both breasts there are elongated, raised firm plaques with clawlike lateral projections. Some of the lesions have been treated with roentgen rays and radium, and they present signs of radiodermatitis.

The first lesion to appear was that on the left arm, following vaccination for smallpox.

An apparently identical twin sister has similar multiple keloids, which also began after vaccination.

The case is presented because of the unusually large multiple keloids, because of the appearance in probably identical twins and for suggestions as to therapy.

DISCUSSION

DR. FRED WISE: It is generally known that treatment is useless in cases of this kind, and all one can say is that it is a tragedy for a person to have keloids of this extent and size. Excision is followed by more keloids, sometimes larger than the original ones, and radiation therapy is of no avail for lesions of this size and thickness.

DR. EUGENE F. TRAUB: Dr. Wise has covered the main points, and I just wish to touch on those on which there could be a possible difference of opinion. Several of the largest lesions, even though located on the back, where the procedure might be painful, might possibly be excised and the area promptly irradiated. The irradiation should follow immediately after the removal of the lesion and be continued in sufficiently large dosage to prevent a regrowth, even though mild sequelae of irradiation might result from such extensive therapy. It would be impossible to get much of a result by irradiation in a case of this type, in my opinion, without some sequelae.

DR. DAVID BLOOM: I shall follow the advice of Dr. Traub and treat the keloids surgically, followed by roentgen irradiation. In looking over the literature in regard to keloids in several members of the same family, I found four references, one by Hutchinson, in 1879, who reported such lesions in three generations of a family, and one by Kaposi, in three sisters. The statement of the patient that the first keloid appeared in each twin soon after vaccination seems to me of interest.

A Case for Diagnosis (Lupus Erythematosus? Chloasma?). Presented by DR. JACK WOLF.

V. C., a woman aged 23, was admitted to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, with an eruption of three years' duration on the cheeks.

The eruption first manifested itself in the form of red spots, following a sunburn. These became brown and increased in size.

There is a butterfly-shaped lesion on the cheeks and extending across the nose, consisting of deeply pigmented macular lesions covered with fine adherent scales.

According to a biopsy section from this area the disease was reported as lupus erythematosus.

DISCUSSION

DR. ISADORE ROSEN: I am not inclined to agree with the diagnosis as presented, for there are no clinical features which would fit in with lupus erythematosus. All

that is present is a symmetric pigmentation on both cheeks, which in all probability is due to some cosmetic the patient has applied.

DR. DAVID BLOOM: I agree with Dr. Rosen that a diagnosis of lupus erythematosus should not be made in this case merely because of the butterfly configuration. I believe that this hyperpigmentation has followed some dermatitis. As to the occurrence of pigmentation in lupus erythematosus, I have observed a number of cases in which pigmentation was pronounced, and I believe that this association is not rare.

DR. EUGENE F. TRAUB: In this case it is difficult to arrive at a clinical diagnosis, because the findings are not clearcut. There appears to be some inflammatory reaction and scaling and some slight pigmentation. How much of the pigmentation may be due to the naturally dark type of skin of the patient is difficult to surmise. For these reasons, I do not believe that this is a case of chloasma, as one does not ordinarily see inflammation and scaling as part of this process. Contact dermatitis could not be excluded, nor can the diagnosis of lupus erythematosus. It would appear to me to be necessary for Dr. Wolf to exclude entirely all possible contact irritations before a diagnosis of lupus erythematosus could be established.

DR. MAX SCHEER: When the patient first presented herself at the clinic, the diagnosis favored was chloasma. A biopsy specimen showed the picture of lupus erythematosus. The pigmentation may be due to the color of the patient, who is a Puerto Rican and has the type of skin that tends to pigment.

DR. FRED WISE: After what Dr. Scheer has just said, it would be presumptuous to say that the patient's eruption is not lupus erythematosus, and yet I am greatly prejudiced against that diagnosis. It is a well known fact that the poorer class of Latin Americans uses cosmetics of inferior grades, which often contain mercury. An entire volume has been written on this subject by an Argentine dermatologist. He explained that in nearly every one of these cases the cause of the pigmentation is some form of cosmetics or the persistent use of them rather than the cosmetic itself. The history given me by the patient is that she had no redness at all preceding this eruption. She said that there was little pigment, but she gave no history of eruption that would make one think of lupus erythematosus. In spite of all that has been said, I still believe that, if she did have lupus erythematosus and was cured, all she now has is pigment from cosmetics. Maybe the cosmetics were used to conceal the lupus erythematosus, but I should certainly not make a diagnosis of lupus erythematosus on present appearances.

DR. JACK WOLF: There are many controversial features in this case and many factors that tend to favor the diagnosis of lupus erythematosus, namely, scaling, some erythema and the history, which, as the patient gave it to me, was that a few red spots developed following a sunburn. A positive clinical diagnosis of lupus erythematosus was not made, but that possibility was entertained on account of the distribution and the history. Much to my surprise, the histologic diagnosis confirmed the probability of lupus erythematosus. Chloasma, cosmetic dermatitis and dermatitis venenata will not give the histologic picture of lupus erythematosus; so there is at least reasonable ground for entertaining that diagnosis.

LOS ANGELES DERMATOLOGICAL SOCIETY

A. Fletcher Hall, M.D., *Chairman*

Clement E. Counter, M.D., *Secretary*

April 10, 1945

Necrobiosis Lipoidica Diabeticorum. Presented by DR. HAL E. FREEMAN.

M. D. B. is a woman aged 36 years. She has had diabetes mellitus for eight years. The present lesions on the right leg and foot have existed for five years.

Three lesions are present. One is on the anterior surface of the right leg, halfway between the knee and the ankle. It is slightly raised, with telangiectasia and a yellowish red color. It is oval, about 4 by 7 cm. in its diameters, and in the upper middle portion of this lesion is a healed ulcer about 2 cm. in diameter. Another lesion is on the dorsum of the left foot. It is a smaller but not ulcerated tumor, and it is located in an old traumatic scar. A third lesion is on the left shoulder. It is a smaller and less highly colored tumor.

The blood cholesterol level has been as high as 334 mg. per hundred cubic centimeters, and the blood sugar level has been 350 mg. per hundred cubic centimeters. This was about one year ago. This patient is especially presented again after six months to show the benefit the Aloe vera leaf dressing has been in the healing of the ulcer.

Necrobiosis Lipoidica Diabeticorum. Presented by MAJOR S. B. MAY (by invitation).

E. W. is a woman aged 22 who has moderately severe diabetes, which has been poorly controlled. Her present illness began three years ago, when a red patch appeared on the upper anterior surface of the right leg. This spot has persisted and gradually enlarged. There are no symptoms. It has never ulcerated.

The patient is a thin, undernourished, pale woman. On the upper anterior part of the right leg on the crest of the tibia are three more or less disconnected oval patches, which are defined. These areas are flat and slightly depressed and have a pale mottled appearance. The centers tend to be yellow with pink to red margins. Central scarring and fine scaling are present. The skin is mildly thickened and indurated. The lesions are not tender.

The blood sugar content has fluctuated from 47 to 532 mg. per hundred cubic centimeters. The blood cholesterol level was 350 mg. per hundred cubic centimeters.

A recent biopsy specimen showed an area of necrosis in the dermis, which was bordered in most places by narrow zones of large mononucleated cells having pale or fine foamy cytoplasm. The surrounding dermis showed infiltration by round cells and focal areas of lymphocytes. There was moderate flattening of the epidermal pegs. Near the base of the specimen there was an artery which showed muscular thickening of its walls. The epithelium was not changed. Stains for fat showed areas of fat extending into the dermis. There were a few scattered cells containing small deposits of fat. The treatment has included careful diabetic management for five weeks in the hospital. Improvement has been shown by the lesions becoming less defined and not so deeply colored.

DICUSSION OF THE PRECEDING TWO CASES

DR. WILLIAM MULVEHILL: Both these cases are instances of necrobiosis lipoidica diabeticorum. They are not exactly typical clinically, because of the large amount of infiltration in both of them and the color. Dr. Freeman's patient did not have the yellow appearance that a patient with necrobiosis lipoidica diabeticorum should show. Both patients have had high blood cholesterol levels. In the cases of necrosis that I have seen, the higher the cholesterol level in the blood, the more prominent was the cutaneous lesion. I believe that the infiltration and the color in both lesions are due to the high cholesterol content of the blood.

DR. NELSON PAUL ANDERSON: I was interested some time ago in seeing an article by Dr. John Harris, of New York, written before Dr. Urbach described necrobiosis lipoidica diabeticorum. Dr. Harris undoubtedly has described necrobiosis lipoidica diabeticorum under the title of Xanthoma Diabeticorum; An Unusual Process of Involution (Goldstein, E., and Harris, J.: *Am. J. M. Sc.* **173**: 195 [Feb.] 1927). It goes to show that cases of this disease were seen before Urbach called attention to them, but physicians called the disease by different names.

DR. HAL E. FREEMAN: Most dermatologists do not expect to find foam cells in the biopsy specimen from a case of necrobiosis lipoidica diabeticorum. If they

do see them, they think of xanthoma diabeticorum. In the last few months some one has written a long article in the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY on what he calls necrobiosis lipoidica diabeticorum with foam cells, and I did not see foam cells in the section from Major May's case. If I had found them, then I should have said that it was xanthoma diabeticorum, but I did not see them, so I think that his case is also a case of necrobiosis, as presented.

DR. J. WALTER WILSON: The Wuecher type of atrophy shown in the slide belongs to necrobiosis lipoidica diabeticorum and not to xanthoma diabeticorum.

MAJOR S. B. MAY (by invitation): There are two minor points that led me to question the diagnosis a bit. One was the asymmetry of the lesions. The lesions are solely on the right leg. The other was the improvement that the patient showed during a five week period in the hospital, where her only treatment was diabetic management. The lesions are now less prominent than before, with less erythema in the borders.

Leukoderma Acquisitum Centrifugum. Presented by DR. SAMUEL AYRES JR.

G. H., a boy aged 14, has had a number of moles scattered over the body for many years. Two of these lesions have undergone a progressive depigmentation in the past year. The lesion on the right side of the upper part of the back was originally dark, but during the past year the lesion became slightly more inflamed and more swollen and has gradually lost pigment, until now only a small central area is pigmented. The lesion on the right temple has similarly undergone a gradual loss of pigment during the past year.

There are a large number of brown moles ranging in size from that of a split pea to nearly that of a dime, which are flat and slightly elevated. These are scattered over the trunk, arms, neck and face. On the right side of the upper part of the back is a red brownish, slightly elevated mole the size of a split pea surrounded by a wide depigmented zone. Higher on the back is an oval, slightly thickened brownish mole half the size of a dime, within which are several irregular almost black streaks. At the lower right border of this mole is a small depigmented area. On the right temple within the hair line is a half dime–sized oval area with a pea-sized brownish slightly pigmented portion and a broad zone of depigmentation including white hair surrounding it.

DISCUSSION

DR. KENNETH STOUT: One wonders about the mechanism in which pigment is formed in one part with a reduced amount of pigment in other parts.

DR. M. E. OBERMAYER: I should like to call Dr. Ayres's attention to the presence of a hyperpigmented macular lesion in the neighborhood of the leukoderma; that lesion is a lentigo and should be investigated for the possibility of early melanomatous changes.

DR. SAMUEL AYRES: One ordinarily does not get a chronologic picture of how these lesions develop. According to the mother, these lesions were at one time all pigmented moles. Then apparently the one most pronounced on the back became somewhat inflamed, and then it began to lose pigment except in the center. The other moles have gone through a similar process. They all began as moles and then became inflammatory; then the pigmentation disappeared peripherally, leaving a central brown spot. The center is more erythematous than it is pigmented.

A Case for Diagnosis (Parapsoriasis with Pigmentation; Urticaria Pigmentosa?). Presented by DR. MAXIMILIAN E. OBERMAYER.

On N. F., a woman aged 26, three months ago an eruption appeared at the sides of her neck and within two weeks spread to cover the areas as seen today.

There is a generalized papulosquamous eruption which covers the body from the neck down to the soles, and it consists of closely set small papules. Some of these are prominent, erythematous and slightly infiltrated and show fine scaling.

The majority are maculopapular and hyperpigmented. No "whealing" can be elicited by friction.

The lesion removed for biopsy from the medial surface of the right thigh was one of the scaling papules. The section showed an epidermis with considerable hyperkeratosis and parakeratosis. There was slight follicular plugging as well as a mild degree of spongiosis in the prickle cell layer. The dermis was edematous and filled with a massive cellular infiltrate, which blended with a basal cell layer of the epidermis and was arranged perivascularly in the upper and middle layers. The infiltrate consisted mainly of lymphocytes. There were some plasma cells and only a few larger cells with massive nuclei.

DISCUSSION

DR. W. H. GOECKERMAN: Most of the members debated in their minds a number of diagnoses, and urticaria pigmentosa possibly came into consideration as well as pityriasis lichenoides chronica. I first thought that it was the latter; then, on looking closer, I saw that the entire body was involved. I asked the patient how long it had been present, and she said three or four months. I see no reason why one should doubt her statement. Despite the unusual characteristics, I think that it is pityriasis lichenoides chronica.

DR. ANKER K. JENSEN: One should not overlook the possibility of a drug eruption. She told me that she had taken Midol (a proprietary mixture containing approximately 0.462 Gm. of acetylsalicylic acid, 0.016 Gm. of cinnamyl ephedrine and 0.052 Gm. of caffeine) for a number of years for some menstrual disturbance. The appearance, distribution and onset are consistent with a drug eruption.

DR. M. E. OBERMAYER: Though I presented the case purposely under two possible diagnoses so as not to bias your judgment, there was not a doubt in my mind that the disease is a nonvarioliform variety of Haberman's pityriasis lichenoides et varioliformis acuta, with an unusual degree of postinflammatory pigmentation. There were a number of factors which aided in ruling out the possibility of urticaria pigmentosa, such as the clinical course of the individual lesions, which pass from an acute erythematous to a scaling stage and finally flatten out to leave hyperpigmented macules; the absence of "whealing" on friction and of mast cells in the section, and the age of onset. I appreciate Dr. Jensen's suggestion of a drug eruption; though I do not think that his assumption is correct, it has taught me to be more insistent in taking a history of medication.

Perforating Ulcer of the Foot in Two Sisters. Presented by DR. SAMUEL AYRES JR.

The family history of V. E., a woman 27 years of age, shows that a sister has had pulmonary tuberculosis, a brother has diabetes and another sister has a lesion of the same type as that presented by the patient. Another brother has some type of mild "paralysis," which has been diagnosed as Charcot-Marie-Tooth type of paralysis. Another brother also has some type of undiagnosed paralysis. Their father had one foot amputated when he was still young, for some unknown cause.

The perforated lesion on the right sole is of four years' duration. It appeared first as a callus on the ball of the right foot, and it persisted for many years. About four years ago a tiny opening appeared, which refused to heal. Five months ago the lesion developed into the present ulceration. The patient says that the lesion is moderately painful at times. Previous treatment consisted of a sulfonamide gel preparation applied locally. Two radium treatments were given one year ago, which did not alter the appearance of the lesion.

On the ball of the right foot is a large callus. In the middle of this callus is a deep ulcer smaller than a dime in size, showing sluggish granulations and a slightly serous discharge. The callus and the ulcer are raised on a puffy, swollen base.

All deep tendon reflexes are normal. The roentgen ray examination of the foot showed old fractures of the third and fourth metatarsals with good osseous union.

The fourth metatarsal is somewhat shorter than normal. The great toe is angled outward, showing early formation of a bunion. There is no evidence of periostitis or of osteomyelitis. The Wassermann, Kline, Eagle and Hinton tests all elicited negative reactions. The blood sugar level was 86 mg. per hundred cubic centimeters.

DISCUSSION

DR. NELSON PAUL ANDERSON: There is a definite indication of a familial tendency, and, while I do not believe that ordinary syringomyelia runs in families, there is a group of familial cases reported in the French literature. These cases occurred in a part of France, possibly Brittany, where a syringomyelia-like syndrome has been present in certain families for a hundred years. I believe that these presented cases belong in that category. They are examples of familial syringomyelia. The other member of the family who presents a Charcot-Marie-Tooth type of atrophy has a different clinical picture than that presented by the two women.

DR. SAMUEL AYRES: These patients are interesting because they are sisters having similar lesions and they have brothers and a father who have paralysis and trophic disturbances of the lower extremities. In Wechsler's "Textbook on Clinical Neurology," fifth edition, the condition is described as a rather peculiar syndrome with a type of atrophy which is difficult to correlate with the underlying pathologic changes. Degeneration has been found in the posterior columns, in the anterior horns and roots and in the peripheral nerves. The disease is probably heredodegenerative. It is commoner in men and may occur in several members of a family. Perforating ulcer of the foot is mentioned as one of the complications of the disease. The father of these patients at an early age had one foot amputated for some disorder, and the amputation wound remained chronic for many years. As far as diabetes is concerned, I think that it can be ruled out. The fasting blood sugar level was 86 mg. per hundred cubic centimeters of blood. There is no obvious neurologic manifestation in either of the sisters presented.

Book Reviews

Human Torulosis: A Clinical, Pathological and Microbiological Study; with a Report of Thirteen Cases. By Leonard B. Cox, M.D., and Jean C. Tolhurst, M.Sc. Price, 25 shillings. Pp. 150, with 67 illustrations. Melbourne: Melbourne University Press, 1946.

In this book the authors report 13 cases of torulosis of the central nervous system, in some of which the condition was associated with torulosis of the lungs and subcutaneous tissue, syphilis, Hodgkin's disease or pulmonary tuberculosis. The detailed study of their own material supplemented by a review of a large literature forms the basis for a discussion of torulosis of various organs, its signs, course, prognosis and differential diagnosis. This excellent study includes the central nervous system, the respiratory system, the lymphatic system, the skin and mucous membranes, the bones, the joints and other tissues. A special chapter is devoted to the microbiology of Torula histolytica, its structure in tissues and in cultures, its resistance to heat, its viability and its antigenic properties. Another chapter deals with experimental torulosis in animals—mice, rats, guinea pigs, rabbits, monkeys, cats and dogs. Pathologic changes of human and animal torulosis in various organs and tissues are described. The discussion of the laboratory diagnosis of the disease includes the technic of examination of cerebrospinal fluid, sputum, nasopharyngeal secretion, blood, urine and skin, the tests of the skin and the serologic reactions. In the last two chapters are the description of the sources and routes of infection and the treatment of the disease. Illustrations are excellent. There are numerous roentgenograms of the lungs and pictures of gross and microscopic specimens of various organs of human beings and animals with torulosis and of cultures of the fungus. This book contains a wealth of original observations and a systematic review of a large literature and is a most valuable contribution to the knowledge of this rare, grave and relatively little known disease.

News and Comment

GENERAL NEWS

A meeting of the Society for Investigative Dermatology will be held on June 10, 1947, at Atlantic City, N. J.

DEATHS

Dr. Isaac R. Pels died in Baltimore on Feb. 4, 1947.

Dr. Ernest Dwight Chipman died on Dec. 4, 1946.

Dr. Arthur Whitfield's death was announced in London, England, on Feb. 4, 1947.